British Journal of Diseases of the Chest

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PHILIP ELLMAN

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J. R. BELCHER

Volume LIV No. 2 April 1960

A Symposium on Disordered Pulmonary Function held at the Queen Elizabeth Hospital, Birmingham on October 23rd and 24th 1959

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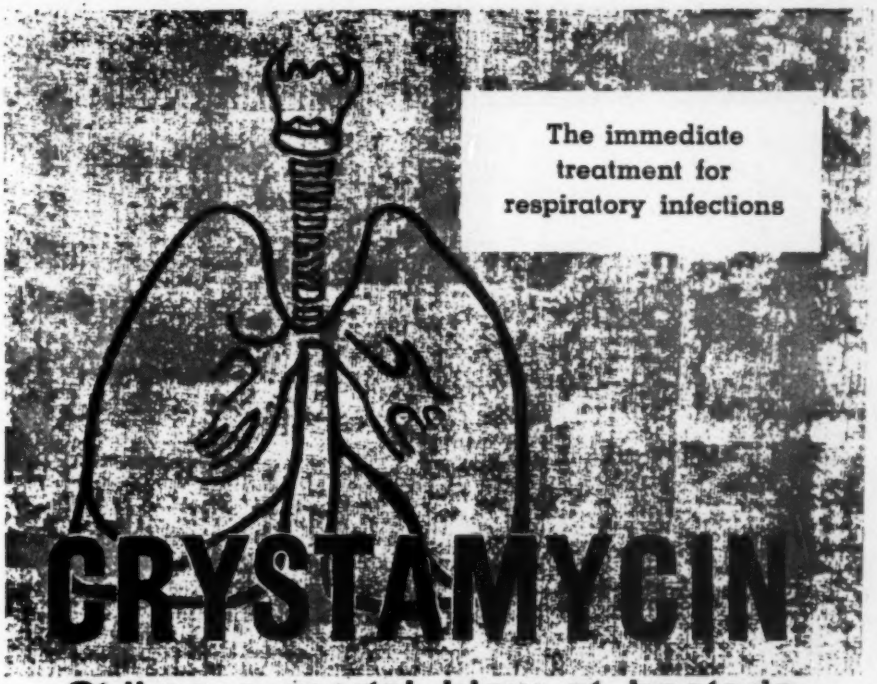

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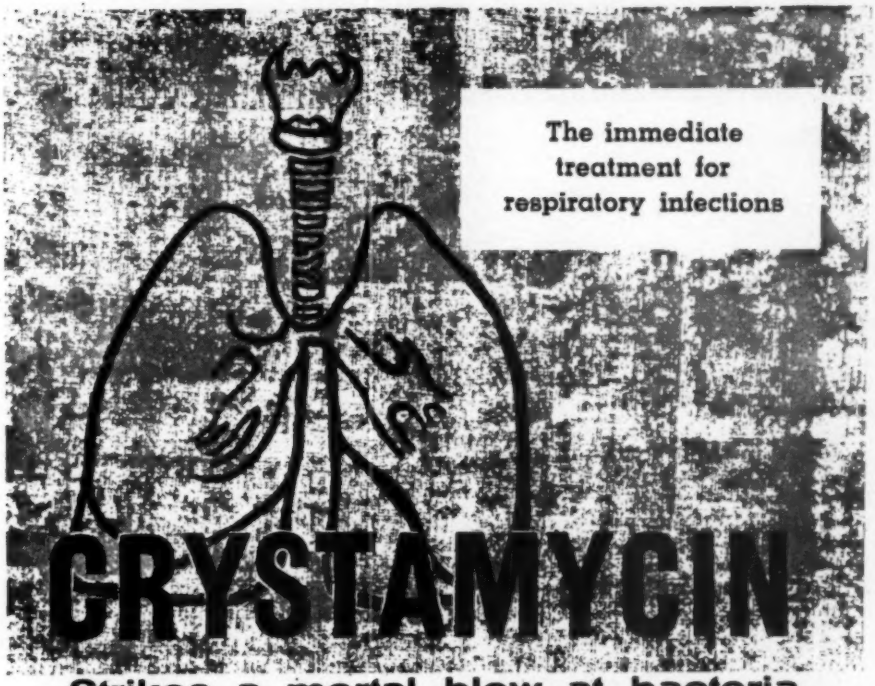

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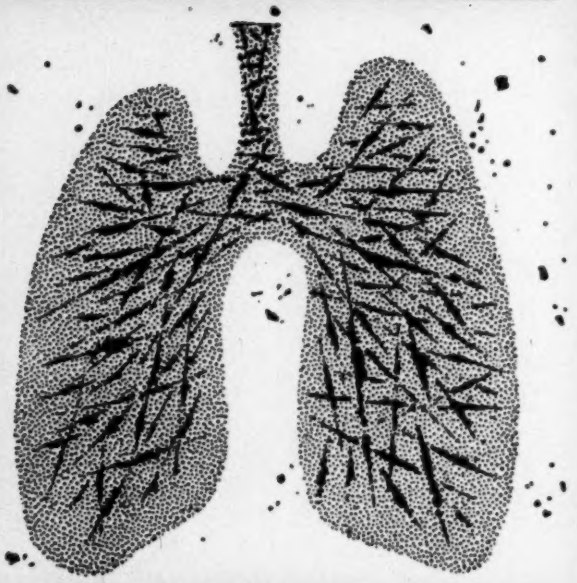

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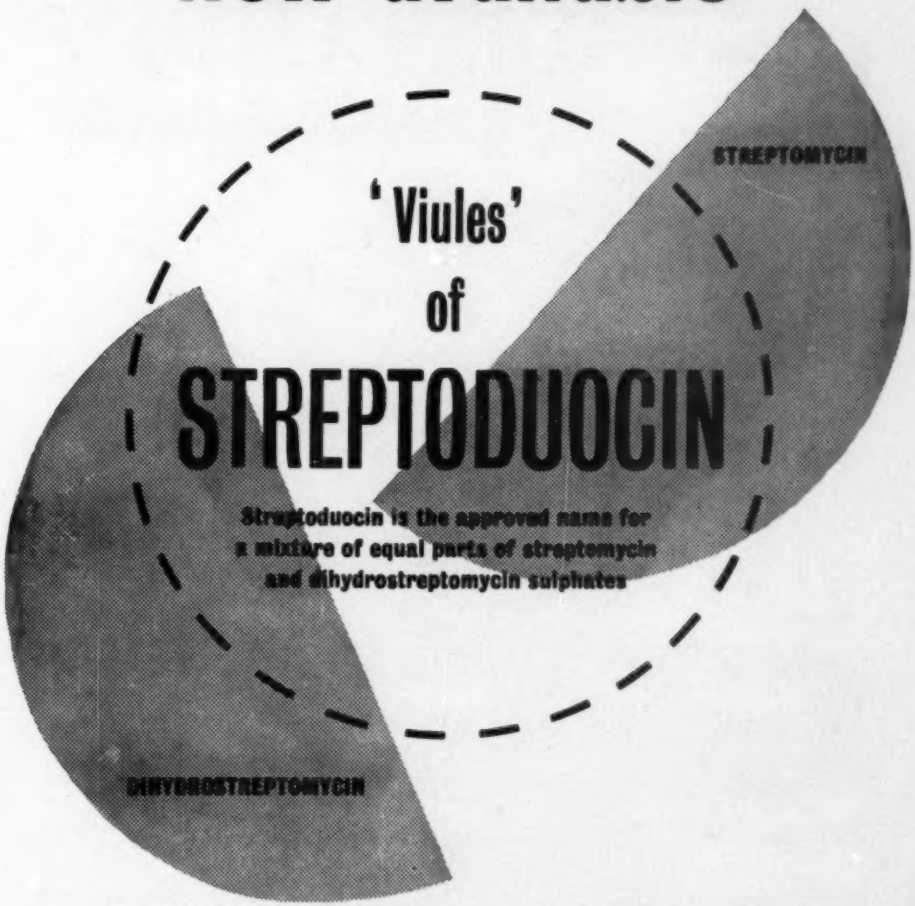

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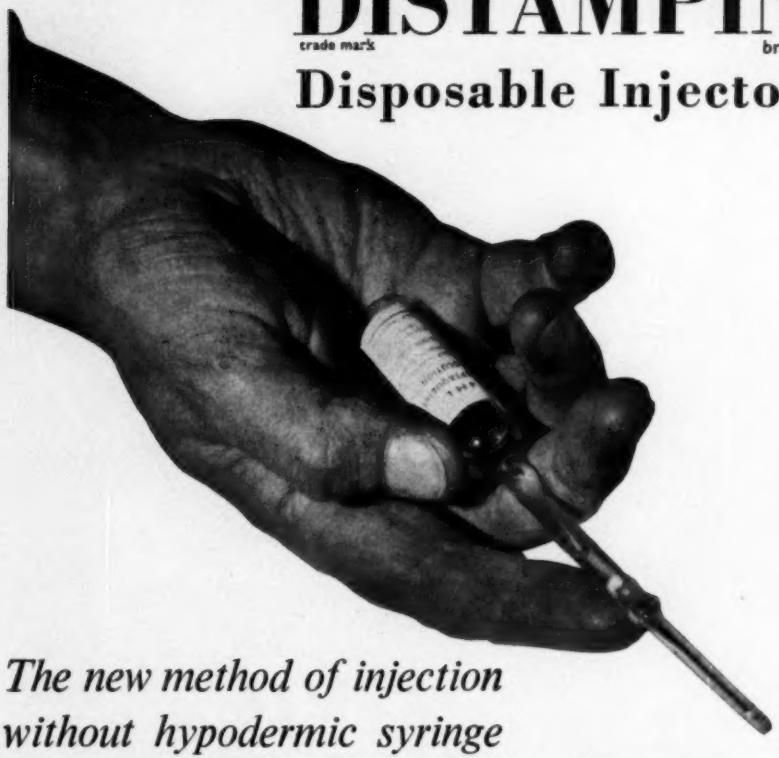

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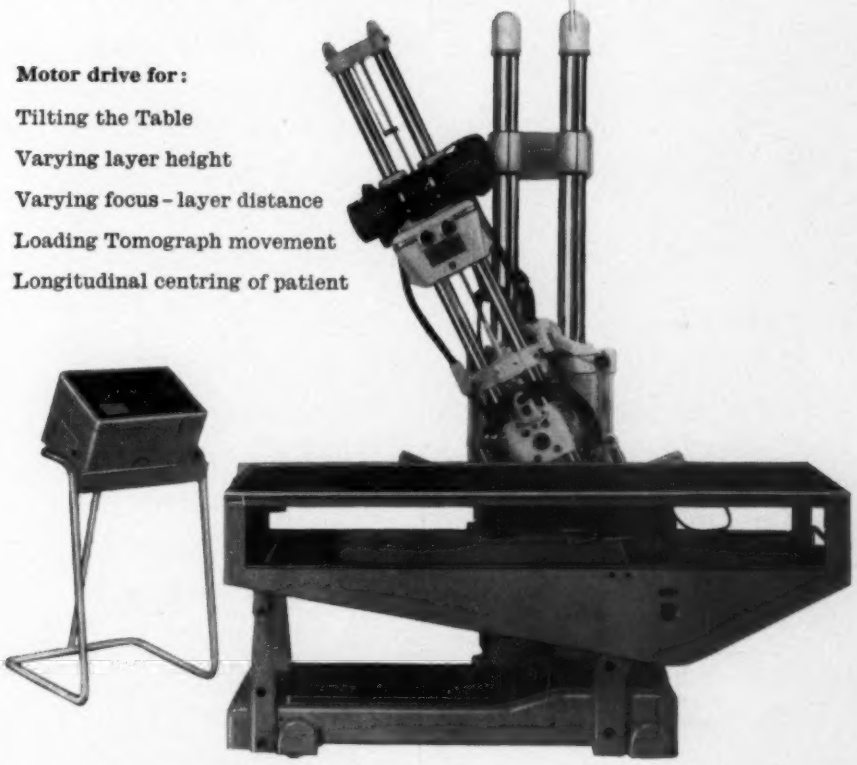

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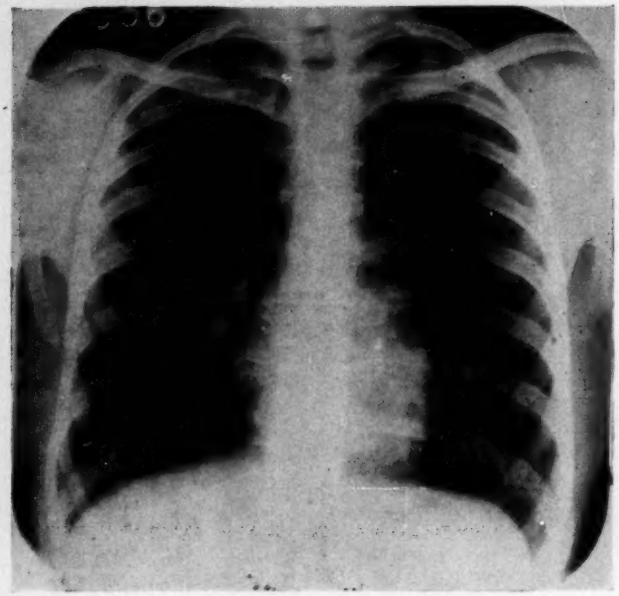

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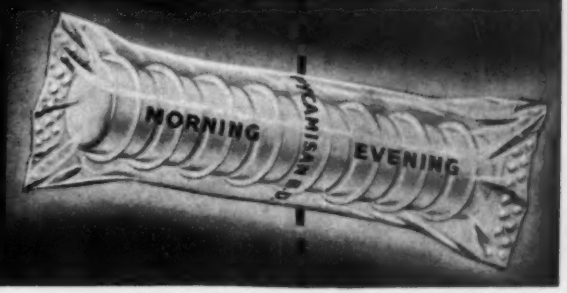

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FOREWORD

THIS issue consists entirely of a Symposium by distinguished experts on "Disordered Pulmonary Function" held under the auspices of the Faculty of Medicine of the University of Birmingham. The practical no less than the theoretical importance of methods of assessment of respiratory function cannot be over-emphasised. Advances in this subject are occurring so rapidly that the contribution of research to the clinical field becomes increasingly important. Highly specialised techniques are being developed and should prove of the greatest value to research workers no less than to practising clinicians.

It is hoped that this issue, with its authoritative contributors and its references to existing published work, will be invaluable to all those interested in this newer study.

P. E.

Brit. J. Dis. Chest (1960) 54, 106.

The Assessment of Respiratory Function

SURVEY OF THE PROBLEM

By W. Melville Arnott

From the Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Birmingham

In opening this Symposium my task is to survey briefly the assessment of respiratory function and to outline the ways in which disease may alter this. The detailed discussion of the various aspects of the subject will then be considered by those better qualified than I.

The last quarter of a century has seen a remarkable development of the quantitative study of the numerous characteristics of respiratory function (Comroe *et al.*, 1954). Indeed, respiration lends itself to such studies, but the interpretation of such data has proved, in general, harder than its collection.

Respiratory function is concerned with homeostasis in respect of arterial oxygen and carbon dioxide and its range of variability is set by the demands of metabolic activity and to a less extent by the share it takes in maintaining the stability of arterial hydrogen ion concentration.

Physiologically respiration can be divided into three zones:

(*a*) *Ventilatory* concerned with the maintenance of alveolar concentrations of oxygen and carbon dioxide such that the tension of the former is sufficiently above that of the mixed venous blood to saturate hæmoglobin in its passage through the pulmonary capillaries, and the tension of the latter is sufficiently below that of mixed venous blood to abstract that volume of CO_2 required by the prevailing metabolic exchange ratio (R.Q. *circa* 0·8).

(*b*) *Diffusion* concerned with the entry of oxygen from the gaseous phase in the alveoli into the liquid phase and its passage to the haæmoglobin molecules and the transit in the reverse direction of carbon dioxide from its solution in plasma to the gaseous phase in the alveoli.

(*c*) *Perfusion* zone concerned with the amount and the rate of flow of blood in that portion of the pulmonary capillaries which constitutes the internal extremity of the diffusion pathway.

Assessment of respiratory function consists of a combination of clinical observations (including history), functional measurements, and structural studies by radiology. These can be considered in relation to the three physiological zones.

Ventilation

Historically the statics of lung volumes have been studied since the time of Hutchison (1846) and the vital capacity has been a common measurement for fifty years, indeed is still sometimes the only measurement made. An important advance was the introduction of measurement of the residual volume. With

this value and a spirogram of normal and vital capacity breathing, the total lung volume and its subdivisions can be calculated. There are two methods of measuring the functional residual capacity from which the residual volume can be deduced; these are the open circuit nitrogen dilution method of Darling *et al.* (1940) and the closed circuit helium dilution method of McMichael (1939). A complete picture of the divisions of lung volume enables, among other things, a ready differentiation between the reduced vital capacity with increased residual volume and a slight increase in the total lung volume such as is seen in emphysema, and the picture of reduced vital capacity and total lung volume, with normal residual volume and a greatly reduced inspiratory reserve capacity such as is seen in individuals whose lungs are stiffened by some diffuse process such as sarcoidosis.

The transition from static to dynamic study of ventilation was gradual and consisted in the first instance of a spirographic tracing taken on a comparatively fast moving drum. The slowing of the expiratory curve and the steady ascent of the resting respiratory level during fast breathing soon become recognised as characteristic of emphysema and are associated with the "air trapping" which is a feature of this disorder.

The development of dynamic studies was for a time handicapped by the inadequacy for this purpose of the Benedict-Roth type of spirometer. This is due to the inertia of the moving parts and the fact that the apparatus has a resonance frequency of the order of 1 cycle per second which imposes gross inaccuracy during rapid breathing. These difficulties have been successfully overcome by the spirometer designed by Bernstein *et al.* (1952).

Dynamic ventilatory tests consist essentially of a measurement of the amount of air that the respiratory mechanism can move per unit of time. In its simplest form it consists of asking the subject to breathe as hard and as fast as he can and to collect expired air (without any intervening valves) in a Douglas bag (or a suitable plastic bag of the Douglas type). Patients can usually keep up such rapid breathing for some 12-15 seconds; the period of their breathing is timed, the volume of expired air measured and the result expressed in air respired per minute. The normal adult can breathe 120-150 litres per minute. Developments of this simple test include the recording on a suitable spirometer of such maximal breathing and the controlling of the frequency factor by asking the patient to breathe as deeply as possible at rates of 30 to 70 times per minute as dictated by a metronome.

A further development was the measurement of the volume/time characteristics of a single maximal breath (Kennedy, 1953). This has led to a bewildering series of measurements, such as the volume expired during the first second of expiration or the volume expired during a known period about the middle of expiration. This has culminated in a very useful simple device developed by Martin Wright (Wright and McKerrow, 1959). It is essentially an anemometer through which the patient expires as fast as he can and a needle on its dial moves to the maximum velocity attained. This is termed the peak expiratory flow rate (P.E.F.R.). Normally adults attain velocities of the order of 500 litres per minute.

With regard to these dynamic ventilatory tests a great deal of work has been done on the measurement of experimental errors, learning factor and correlation with anthropometric data such as sex, age, weight, height and stem height. Various prediction formulæ have been devised and there has sprung up a crop of ratios of observed as compared with predicted. Through it all, however, there emerges a strong impression that the Wright meter* represents perhaps the most sensitive single test of ventilatory capacity that is within the competence of the busy clinician.

The magnitude of impairment of function imposed by the spasmodic airway obstruction of such conditions as asthma can be assessed by carrying out these tests before and after the administration of an antispasmodic such as iso-propyl-nor-adrenaline.

An important criterion of ventilatory efficiency is the uniformity or otherwise of the distribution of a breath. Normally distribution is comparatively uniform as is shown by the rate with which a person comes into equilibrium with a closed circuit containing helium as the marker gas, in fact the rate of helium dilution is very nearly exponential, indicating uniform dilution (Bates and Christie, 1950). The same characteristic can be demonstrated by the nitrogen washout test in which the patient breathes pure oxygen, and the nitrogen content of each successive expiration shows that the oxygen distribution is remarkably uniform (Darling *et al.*, 1944). A more convenient but somewhat expensive way of measuring air distribution is provided by the nitrogen meter, which is a device which, with a suitable recorder, gives an accurate tracing of the nitrogen content of a fast flowing gas stream. This instrument samples continuously the gas passing through a mouthpiece. The patient takes a maximum breath of oxygen and a tracing is made of the nitrogen content of the following maximal expiration. In the normal person the tracing of the nitrogen content of the expirate is, after the dead space is washed out, a very nearly horizontal plateau at about the 40 per cent. level. This is in striking contrast to the progressive ascent of the tracing seen in emphysematous individuals in whom gas distribution is greatly distorted (Comroe and Fowler, 1951).

Diffusion Zone

Measurements in this field centre around the rate of passage of oxygen from alveoli to blood and of carbon dioxide from blood to alveoli. The rate of diffusion of a gas through the liquid phase depends upon the tension gradient, the length of the diffusion pathway, the specific solubility of the gas and its specific diffusibility. Owing to its high solubility and diffusibility carbon dioxide diffuses about twenty times more rapidly than oxygen; in fact nearly as much carbon dioxide as oxygen is exchanged per unit of time at a mean tension gradient of about 3 mm. Hg as compared with a mean oxygen tension gradient of the order of 30 mm. mercury. The commonly used factor, termed the Diffusion Capacity ($D_{L_{O_2}}$), is the amount of oxygen absorbed per unit of time per millimetre tension gradient. One of the best methods of measuring this

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requires the estimation of the gas tensions in the alveoli and in the pulmonary capillary blood. Fortunately in this respect a sample of systemic arterial blood can be regarded as having a CO_2 tension identical with that of pulmonary capillary blood. By a series of ingenious calculations too detailed to be dealt with here, combined with the device of making measurements while breathing room air and also air containing only 14 per cent. oxygen, it is possible to calculate the gradient of oxygen across the alveolar wall and to differentiate that portion of the gradient which is due to the length of the diffusion pathway and that portion which is due to the variable amount of blood which bypasses respiratory capillaries, the so-called admixture or shunt factor (Riley *et al.*, 1951a). Unfortunately, when presented with a reduced pulmonary diffusion capacity there is no direct way of estimating how much of this is due, on the one hand, to reduction in the area of the blood/gas interface or, on the other hand, due to increase of the diffusion pathway. Fortunately this limitation is not so serious as it seems because collateral information about the patient, such as history, clinical picture, radiological picture, etc., will indicate which dimension is at fault. For instance, if one lung be collapsed owing to a pleural effusion the consequent reduction in diffusion capacity is clearly due to the " area " factor. There are much simpler although somewhat less discriminating methods of estimating diffusion capacity, such as the single breath carbon monoxide method. The affinity of hæmoglobin for carbon monoxide is so high that its tension in blood plasma can be taken as zero. Therefore, in essence, this test consists simply of inhaling and holding for ten seconds a breath containing a small known quantity of carbon monoxide. The difference between the CO content of the breath before and after this 10 second interval gives the amount absorbed (Krogh, 1914-15; Forster *et al.*, 1954).

Fortunately the theory behind diffusion measurement is susceptible to some simple applications. For instance, the fact that carbon dioxide diffuses so much more readily than oxygen means that, whereas a uniform increase of diffusion distance causes arterial unsaturation, it will not impair CO_2 elimination, in fact, it may even facilitate it because the anoxia may stimulate breathing. The discovery, therefore, of a patient with arterial unsaturation but whose arterial blood has a normal or reduced CO_2 content is practically diagnostic of a diffusion defect. This contrasts sharply with states of arterial unsaturation due to alveolar hypo-ventilation (*e.g.* emphysema, etc.) in which carbon dioxide tension of the arterial blood is elevated in order to gain the 6 mm. or so ascendance which enables it to flow into the poorly ventilated alveolar pool with its abnormally high CO_2 content. This is the background of the hypercarbia of ventilatory insufficiency (Arnott, 1959).

Perfusion Zone

The study of this zone is concerned principally with the hæmodynamics of pulmonary blood flow and the relevant measurements are made in the main by cardiac catheterisation. It is in the study of this zone that pulmonary and cardiac physiologists meet. In the absence of shunts the whole of the right ventricular output must pass through the pulmonary vascular bed, and if this

be reduced either by organic obliteration of vessels or by their contraction such as may be induced by hypoxia, then pulmonary pressures tend to rise and the velocity of blood flow through the capillaries increases. The physics of the diffusion of oxygen and the time constants of its combination with hæmoglobin are such that any marked increase in mean velocity of blood flow through the pulmonary capillaries leads to incomplete saturation with some consequent degree of systemic arterial unsaturation.

It is sufficient in this brief summary to say that many pulmonary disorders are associated with pulmonary vascular hypertension (Cournand, 1950).

Ventilation/Perfusion Ratios

An important synthesis of these groups of tests illuminates the concept of the ventilation-perfusion ratio which is fundamental to efficient pulmonary function (Riley and Cournand, 1949). If a pair of lungs, a single lung, a lobe, or for that matter an alveolus, is disproportionately well ventilated as compared with the amount of blood flowing through its capillaries, then more carbon dioxide will be eliminated than oxygen absorbed, while on the other hand if it be poorly ventilated in relation to its blood flow the amount of carbon dioxide eliminated will be much reduced in proportion to the amount of oxygen absorbed. The overall exchange ratio of carbon dioxide to oxygen is set by the metabolic pattern of the whole body and is in the normal person on an average diet around 0·8. Brief respiratory departures from this normal ratio are possible, provided that within a comparatively short time, of the order of minutes, compensation is achieved.

Overall respiratory function is a summation of that of millions of alveoli each with its ventilation perfusion ratio. Although in health this seems to be remarkably uniform it is obviously a delicately adjusted mechanism extremely liable to be distorted by any disease process, in fact by most disease processes which impair either or both ventilation and perfusion. There is, however, great scope for compensation. I will leave others who follow me in this Symposium to deal adequately with this very important ventilation-perfusion concept.

Lung Mechanics

Although developed many years ago by Rohrer (1915), the full recognition of the importance of the study of pulmonary function by accepted engineering principles is a development of the last decade (Fenn, 1951). The mechanism of ventilation is obviously associated with a cyclical pattern of pressure-volume relationships, as indeed is any mechanical device of similar type such as the reciprocating (pump, steam, or internal combustion) engine. An *x-y* plot of simultaneous values of pressure and volume during a single respiration enables quantitative deductions to be made of (1) the resistance of the lung to distension (compliance), (2) the non-elastic resistance to the passage of air through the bronchi, and (3) the viscous resistance offered by the moving of tissue planes. It is possible to calculate the amount of work done in overcoming

elastic resistance and also the amount of non-elastic work done in driving air through the tubes and sliding the various pulmonary tissue planes. All these measurements can be made on the basis of volume displacement of air as measured by a flow meter or a suitable spirometer combined with measurement of intrathoracic pressure, as obtained from a balloon in the œsophagus (Arnott, Butler and Pincock, 1954). Data for the thoracic cage and lungs combined are obtainable by enclosing the patient in a Drinker respirator and substituting external thoracic pressures for intrathoracic pressure.

There are a variety of methods, *e.g.* mechano-optical and oscillographic, for integrating these pressure flow values when they are expressed as rectangular co-ordinates.

From the diagnostic angle these pressure-flow studies differentiate sharply between respiratory disability due, on the one hand, to airway distribution and, on the other, to stiffening of the lungs. In the case of the former, the work required to overcome non-elastic resistance is relatively increased, whereas in the latter case the work done in overcoming elastic resistance is increased; thus the application of engineering principles reveals pathological defects (Christie, 1953).

Practical Organisation

It is not only very helpful to be able to make appropriate measurements of respiratory function, but it is essential to be able to do so in a way that is economical of apparatus, time and assistance. For that reason there is included in the Symposium a contribution on the organisation of a respiratory laboratory which I hope will enable people to get the maximum information with the minimum of effort. This will show that with apparatus consisting of a suitable spirometer, a Wright airflow meter, a blood gas analyser (Van Slyke, Haldane or spectrophotometric) and a gas analyser (Haldane type, *e.g.* Microscholander), and the ability to do arterial punctures, a great deal of useful information can be acquired.

The fact that the CO_2 tension of systemic arterial blood is identical with that of the alveolar CO_2 tension enables an analysis of alveolar air to be used as an indication of arterial CO_2 tension (Collier, 1956). A simplified method of doing this has been devised by Campbell and Howell (1958), which will be described further on in this issue. Its very simplicity bids fair to make it the sort of valuable measurement in respiratory disease that the blood sugar is in diabetes mellitus or the blood urea in renal disease.

Pathological Processes

The pathological mechanisms which interfere with respiration can be usefully grouped according to whether their impact is mainly on the ventilatory, diffusion or perfusion zones.

(*a*) For instance, ventilatory disorder may be due to any disease causing airway obstruction, such as bronchitis, emphysema, asthma, tracheal compression, etc.

(*b*) Any process which interferes with the thoracic cage or pleura, such as gross obesity, scleroderma, kyphoscoliosis, chest wall injury, either accidental or operative, pleural effusion, pneumothorax, thickened pleura.

(*c*) Any interference with neurogenic control, such as barbiturate poisoning, paralytic poliomyelitis, myasthenia gravis, polyneuritis, progressive muscular atrophy, porphyria, muscle relaxant drugs of the curariform type and intracranial injury and disease.

Diseases which cause diffusion defect are those which interpose on a wide scale any new material, be it fluid, cellular or connective tissue, between alveolar air and capillary blood. These include such processes as pulmonary œdema, either acute as occurs in left ventricular failure or more gradual as in chronic pulmonary hypertension of mitral stenosis, sarcoidosis, scleroderma, pneumoconiosis, berylliosis, radiation fibrosis, lymphangitic carcinomatosis, pulmonary histiocytosis, the diffuse pulmonary inflammatory process called the Hamman-Rich syndrome, etc.

The perfusion zone is principally at fault in those disorders which block pulmonary blood vessels, for example multiple embolisation. Most of these processes, while they involve mainly one or other type of function, affect also other functions, so that when one regards a disorder as ventilatory or diffusion in nature one merely indicates the mechanism impaired predominantly.

My comments have been of necessity laconic and superficial but I am sure the necessary depth will be added as the Symposium develops.

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PULMONARY VENTILATION

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The function of the pulmonary ventilation is to maintain concentrations of oxygen and carbon dioxide in the alveoli which will permit the optimal exchange of gas between the alveoli and the blood in the pulmonary capillaries. The alveolar oxygen tension must be maintained sufficiently above the oxygen tension of mixed venous blood for the blood to become adequately saturated with oxygen. At the same time the carbon dioxide tension must be sufficiently below the tension of mixed venous blood to ensure adequate elimination of carbon dioxide as the blood passes the alveoli.

Under most conditions in a subject breathing air, it is found that the alveolar gas tensions vary relatively little. This is true, for instance, during fairly strenuous exercise, when oxygen uptake and pulmonary ventilation are considerably increased, and provides evidence of the remarkable precision of the mechanisms which control the pulmonary ventilation. While remarking this fact, it is not proposed to discuss the regulation of ventilation, but to survey briefly the methods by which the pulmonary ventilation can be measured and the causes and effects of various disturbances of the ventilation as the result of disease.

The earliest studies relating to the ventilation of the lungs were measurements of the static lung volumes, beginning with the vital capacity which was defined by Hutchinson in 1846. Although the static lung volumes are frequently measured, there can be no doubt that, in the past, too much attention has been paid to them in proportion to the useful information they provide. Supplying, as they do, only a gross description of the dimensions of the lungs, they largely describe their anatomy rather than their function. Nevertheless their measurement has some place in the assessment of the effect of disease on the lungs, and they are probably of greatest value in following the course of a disease process in an individual. The range of variation of values for the lung volumes in groups of subjects is large, so that in an individual an observed value must deviate from the predicted mean by a large amount before it can confidently be pronounced abnormal. In the case of one individual, however, repeated measurements can be shown to be repeatable and therefore much smaller changes in serial observations may be regarded as significant.

In the past, some confusion has resulted from the use of various names for the static lung volumes, but the terminology agreed by the committee headed by Pappenheimer (1950) is now in general use. Under this system, components of the total lung capacity which can be subdivided are referred to as capacities, while the subdivisions themselves are termed volumes. Thus the vital capacity is composed of the expiratory reserve volume plus the tidal volume and the inspiratory reserve volume. The inspiratory capacity is the volume of gas which

can be taken in by a maximal breath from the normal expiratory level and is equal to the sum of the tidal volume and the inspiratory reserve volume. The functional residual capacity is the volume of gas remaining in the lungs at the end of a normal expiration. It is subdivided into the expiratory reserve volume and the residual volume, the latter being the volume of the lungs after a maximal expiration.

The vital capacity and its subdivisions are readily measured by means of a spirometer with a slow speed kymograph tracing. The vital capacity may be reduced in such a wide range of conditions that it is without diagnostic value, although serial measurements in one patient may give useful information about the progress of the disease. In order to determine the total lung capacity it is necessary to measure the functional residual capacity. This is most conveniently effected by the closed circuit helium method in which the patient rebreathes into a circuit containing a known initial concentration of helium. The method was originally described by McMichael (1939) using hydrogen as the indicator gas, but helium is now preferred because of its safety. After a short time an equilibrium is reached in which the concentration of helium is the same throughout the lungs and the spirometer circuit. From a knowledge of the initial and final concentrations of helium and the volume of the apparatus, the volume of gas in the lungs may be calculated. The functional residual capacity may also be measured as the total volume of intrathoracic gas, with the aid of the body plethysmograph (Dubois *et al.*, 1956). Under certain conditions the estimates obtained by these two methods may differ, the volume of intrathoracic gas determined by the body plethysmograph exceeding the functional residual capacity measured by the helium dilution method. This is due to the presence of gas which is trapped in the lungs and not in communication with the airways, as in lung cysts or bullæ.

The residual volume, expressed as a percentage of the total lung capacity, is increased in emphysema, and such an increase has sometimes in the past been mistakenly regarded as diagnostic of this condition. This ratio also increases with advancing age, and will also be increased whenever the total lung capacity itself is reduced. These two factors must always be taken into account and it is then clear that an increased ratio of residual volume to total lung capacity does not by any means always signify the presence of emphysema.

The volume of pulmonary ventilation is an important quantity which cannot be determined reliably by inspection of the patient. While it is easy to count the respiratory frequency, the tidal volume cannot reliably be inferred from the apparent range of the chest wall movements. Where the respiratory minute volume is of importance, it should be measured directly. This is a simple procedure, and requires only a respiratory value and mouthpiece and a Tissot spirometer or lightweight Douglas bag and a gas meter. If respiratory frequency is counted at the same time, the average tidal volume is easily calculated. While the pulmonary ventilation at rest is of considerable value, the volume ventilated during exercise is often of greater importance. This can be determined in exactly the same way while the patient is walking at a predetermined speed with the observer carrying the Douglas bag, or perhaps more

conveniently, the patient may be asked to perform a standard step test. The observed pulmonary ventilation may then be compared with previously established normal values under the same conditions.

When considering pulmonary gas exchange, it is important to think in terms of the alveolar ventilation rather than the total ventilation. Measurement of the alveolar ventilation requires knowledge of dead space volume, since alveolar ventilation is equal to total ventilation less the dead space ventilation. The pulmonary dead space is defined as that volume of gas contained in the lungs which does not take part in rapid gas exchange with the blood flowing through the lungs. It includes the volume of gas in the conducting airways and also gas which is contained in alveolar spaces which are not perfused with blood. The dead space may be calculated from the Bohr equation, using carbon dioxide as the indicator gas:

$$\text{Dead space volume} = \frac{F_{A_{CO_2}} - F_{E_{CO_2}}}{F_{A_{CO_2}}} \times \text{Tidal volume}$$

where $F_{A_{CO_2}}$ and $F_{E_{CO_2}}$ are the fractions of carbon dioxide in alveolar gas and mixed expired gas respectively. In many patients with lung disease it is not possible to obtain a sample of alveolar gas and the value for the arterial carbon dioxide fraction is then substituted. It is known that equilibrium is always reached between the carbon dioxide in alveolar gas and pulmonary capillary blood, so that the arterial carbon dioxide tension provides an integrated value derived from all perfused alveoli. The dead space calculated in this way is termed the physiological dead space. If dead space is known, the alveolar ventilation may be determined, since—

Alveolar ventilation = Respiratory frequency × (Tidal volume − dead space volume).

From this relationship it is evident that for a given level of total pulmonary ventilation the alveolar ventilation will be less if respiratory rate is increased and tidal volume decreased or if the dead space volume is increased.

A reduction in the volume of alveolar ventilation results in a decrease in oxygen tension and an increase in carbon dioxide tension in the alveoli. Due to the shape of the hæmoglobin oxygen dissociation curve, the decreased oxygen tension is not associated with a significant diminution in oxygen saturation of arterial blood unless the reduction in alveolar ventilation is profound. The increased carbon dioxide tension is of greater practical importance because it provides a measure of the adequacy of alveolar ventilation, the two quantities being related, since—

Carbon dioxide output = Alveolar ventilation × Alveolar fraction of carbon dioxide.

Thus, if the carbon dioxide elimination remains constant, the alveolar ventilation and alveolar carbon dioxide tension are inversely related. The measurement of arterial carbon dioxide tension is therefore a valuable means of estimating whether alveolar ventilation is adjusted correctly to the current body requirements of the subject. Reduction of alveolar ventilation may be due to depression of the respiratory centre, to interference with the neuromuscular control of the movements of the chest wall, to disease of or injury to the chest

wall, or to disease of the lungs themselves, usually in the form of an obstruction to the conducting airways.

Alveolar hyperventilation results in a decrease of the carbon dioxide tension and an increase in the oxygen tension. The latter change will not produce a detectable alteration in the oxygen saturation of arterial blood in a normal subject breathing air, because of the flat shape of the dissociation curve at this point. In the case of a patient with impairment of the diffusing capacity due to alveolar-capillary block, the hyperventilation which often occurs may, however, raise the alveolar oxygen tension sufficiently to maintain a normal arterial blood oxygen saturation at rest, although unsaturation appears readily on exercise. Unless hyperventilation is severe, the reduction in carbon dioxide tension does not produce symptoms, but once again the measurement of the arterial carbon dioxide tension provides a reliable indication of whether alveolar hyperventilation is present. Hyperventilation is most commonly found in association with anxiety states, but may result from metabolic acidosis or from certain lung diseases, notably those leading to diffuse pulmonary infiltrations. Hyperventilation is also commonly seen during assisted respiration, both during anæsthesia and in the treatment of patients with paralysis of the respiratory muscles.

Finally, in considering the pulmonary ventilation it is necessary to inquire how the alveolar ventilation is distributed within the lung. Ideally the ventilation should be distributed evenly to all of the individual alveoli, and this ideal is closely approached in normal subjects. This is a most remarkable fact and illustrates once again what an efficient machine is the normal lung. In some disease states, and most obviously in emphysema, the ventilation is distributed in a grossly uneven fashion, some alveoli being underventilated, while others are hyperventilated. This uneven distribution of inspired gas results from local variations in the resistance to flow in the airways, and from local variations in lung compliance, the gas flowing preferentially along those airways which have a low resistance. When the ventilation is distributed unevenly a reduction in the arterial blood oxygen tension results, and when the distribution is grossly uneven an elevation of carbon dioxide tension is also found. The reasons for these changes are discussed in the accompanying paper concerning the blood gases.

Evidence of uneven distribution of inspired gas may be found during the estimation of functional residual capacity by the closed circuit method. The rate at which the concentration of helium in the rebreathing circuit approaches the final equilibrium value is slower when the distribution of inspired gas is abnormal, and various indices have been used to describe numerically this delayed equilibrium. The most convenient and simple way of detecting uneven distribution of inspired gas is, however, by the use of the very rapidly responding nitrogen meter in the manner described by Comroe and Fowler (1951). The instrument is arranged to measure the concentration of nitrogen in expired gas at the mouth, following a single inspiration of oxygen. The poorly ventilated alveoli receive little oxygen and at the end of inspiration of the breath of oxygen they still contain a high proportion of nitrogen. The well-ventilated

alveoli, in contrast, have received a high proportion of oxygen and their concentration of nitrogen is lower. During the subsequent expiration the well-ventilated alveoli tend to empty first, and the poorly ventilated ones empty late in expiration. Consequently, the concentration of nitrogen in the alveolar gas, recorded by the nitrogen meter, increases as expiration proceeds. In normal subjects there is hardly any comparable increase in nitrogen concentration and this phenomenon can therefore be used as an indication of the unevenness of distribution of the inspired gas. Although requiring a relatively complex instrument this test is quick and simple to perform.

In conclusion, it may be said that disturbances of pulmonary ventilation are found in many types of lung disease and in disorders affecting the respiratory muscles and their controlling nerves. The volume of ventilation and its distribution are quite easily studied and give information which may be of diagnostic value and which is often essential in the control of treatment.

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MECHANICAL PROPERTIES OF THE LUNG

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The mechanical functions of the lungs are concerned with ventilating the alveoli and aiding venous return to the heart; the mechanical properties of the organ allow this to be done with a very small expenditure of energy. Since the lung is mechanically an integral part of the chest, the properties of the combined lung and chest wall (made up of thoracic cage and diaphragm) are those of functional importance to the body.

Chest Wall and Lungs

Elasticity

When a person inspires a proportion of the vital capacity and then relaxes against a manometer held in the mouth, a positive pressure is recorded. After exhaling from the resting respiratory level a negative pressure is developed. When these pressures are plotted against the corresponding volume, a relaxation pressure curve results (Fig. 1). This line of increasing pressures as the chest volume enlarges characterises the elastic properties of the chest wall and lungs (Otis *et al.*, 1950). No pressure is registered at the normal resting volume, where the traction of the lungs just balances the elastic expansile force of the chest wall. The considerable static elastic pressures at very high and low volumes must normally be balanced by the action of the chest wall muscles. This balance largely determines the value of the vital capacity and other static lung volumes. The maximum respiratory pressures which the chest wall can develop under static conditions are also shown; it can be seen that in assessing the static expiratory power of the respiratory muscles the patient should take a full inspiration first, while the greatest static inspiratory force can only be developed at full expiration. Pressures considerably greater than these can, however, be developed transiently in sneezing or coughing or during movement in forced respiratory manœuvres (Campbell, 1958).

Frictional Resistance

If a subject relaxes and allows himself to be ventilated in a cabinet type of respirator, the pressure changes around the body and the simultaneous lung volume changes which they cause, measured by a spirometer at the mouth, form a pressure-volume loop (Fig. 2). The pressure-volume relationship does not simply move up and down the elastic relaxation pressure curve as the chest is inflated and deflated, since frictional forces have now to be overcome. These are greatest when movement is fastest, at about mid-inspiration where a more negative pressure around the body is required, and mid-expiration where a more positive pressure is necessary to overcome them. The faster the rate the

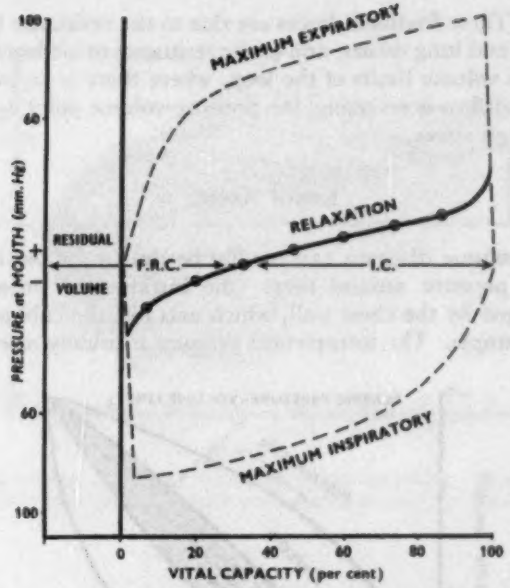

FIG. 1.—Relaxation pressure curve and maximum static pressures of chest wall and lungs. (After Otis, Fenn and Rahn, 1950.)

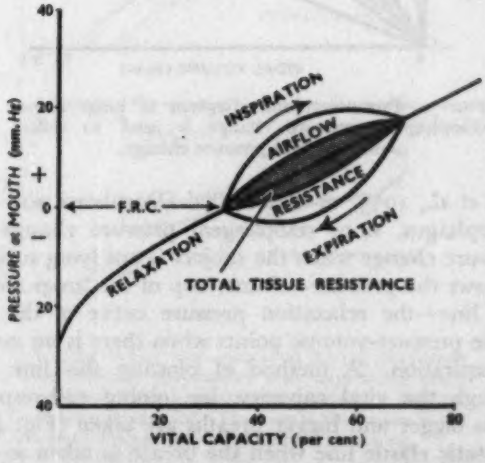

FIG. 2.—Pressure-volume diagram of chest wall and lung during ventilation in a cabinet respirator. Pressures at the mouth, *relative to those around the chest*, are plotted against percentage of vital capacity.

fatter the loop. These frictional forces are due to the resistance to deformation of the chest wall and lung tissues, and to the resistance to airflow in the airways. However, at the volume limits of the loop, where there is no movement since the direction of airflow is reversing, the pressure-volume point again lies on the relaxation pressure curve.

Lungs Alone

Elasticity

A pressure-volume diagram can readily be drawn for the lungs alone by measuring the pressure around them (the intrapleural pressure), as their volume is changed by the chest wall, which acts like the cabinet respirator in the previous example. The intrapleural pressure is usually assessed by means

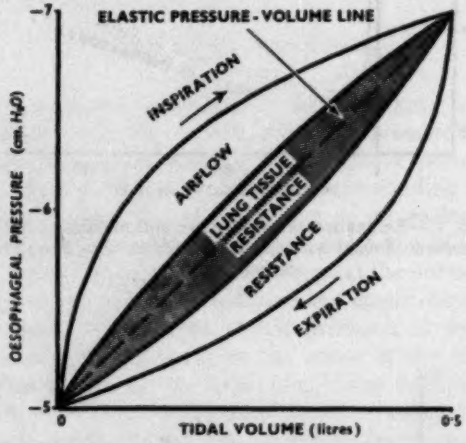

Fig. 3.—Pressure-volume diagram of lungs alone. Œsophageal pressure change is used to reflect intrapleural pressure change.

of an air (Mead *et al.*, 1955) or water-filled (Dornhorst and Leathart, 1952) tube in the œsophagus, since œsophageal pressure change closely reflects intrapleural pressure change when the subject is not lying supine (Ferris *et al.*, 1959). Fig. 3 shows the pressure-volume loop of the lungs alone. The elastic pressure-volume line—the relaxation pressure curve of the lungs alone—is obtained from the pressure-volume points when there is no movement at end-inspiration or expiration. A method of plotting this line under dynamic conditions, through the vital capacity, by joining end-respiratory and expiratory points as bigger and bigger breaths are taken (Fig. 4), may be compared with the static elastic line when the breath is taken so slowly that frictional forces are negligible (Fig. 5). The slope of this elastic pressure-volume line is the lung compliance (litres per cm. water pressure) and must be corrected for the size of the lungs, since a volume of air will cause a bigger pressure change

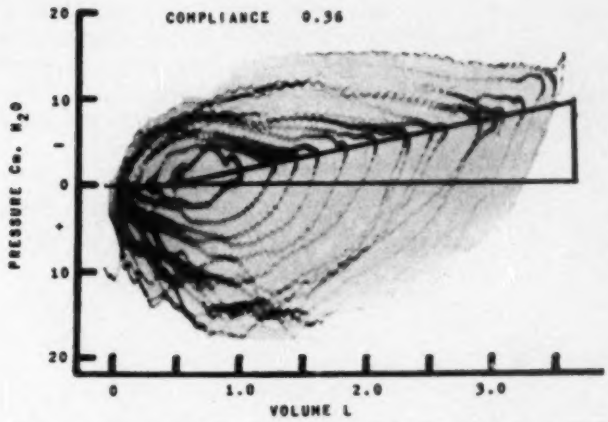

FIG. 4.—Lung elastic line measured during breathing. Static pressure volume points at moments of airflow reversal are joined.

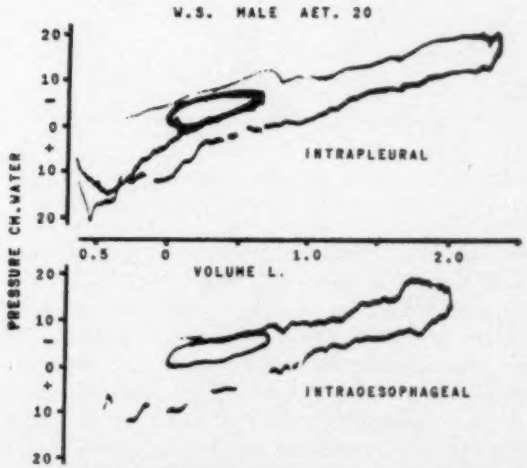

FIG. 5.—Lung elastic line measured during very slow (over one minute) inspiration and expiration using intrapleural and intra-œsophageal pressures. Inspiratory line above expiratory. The loop in the centre is the pressure volume record of normal breathing.

To face p. 120

in a small elastic system than in a big one. The elastic line is always slightly different on expiration than on inspiration, due to a stretch or adaptation effect of the inspiration (Butler *et al.*, 1957). The slow breath of Fig. 5 was repeated using intrapleural pressures in this man who had a shallow spontaneous pneumothorax, and the good correlation between œsophageal and intrapleural pressure changes is shown.

Disease Conditions

The lung compliance has been found to be reduced—the lungs are stiffer—in several different groups of cardio-respiratory diseases. In heart failure—

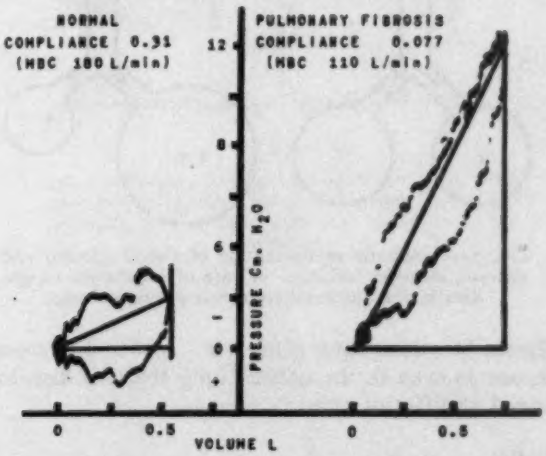

FIG. 6.—Pressure-volume loop in a patient with pulmonary fibrosis, contrasted with a normal loop.

particularly mitral stenosis and left ventricular failure—and in states of acute pulmonary congestion, the lungs become abnormally rigid (Brown *et al.*, 1954). Pulmonary infiltrations and fibrosis (Fig. 6) lead to the same changes. There is also a reduction in lung compliance in any condition where lung expansion and the vital capacity are reduced, as in effusions, chest wall weakness or deformity (Caro and Gucker, 1958). This again seems to represent an adaptive phenomenon, this time to the lack of lung expansion; and though the exact mechanism is unexplained, a reduction in the number of ventilated lung units (Bernstein, 1954) and a hysteresis-like effect in the lung tissues (Hughes *et al.*, 1959) may both play a part. Lung compliance, measured during breathing (Fig. 4), is also reduced in conditions of obstructive airway disease. The explanation of this odd finding in patients with emphysema, where lung elasticity was once thought to be lost, and in asthma, lies in the maldistribution of the gas within the lung in these diseases. Fig. 7 shows that as the rate of breathing is increased, less and less gas has time to pass through partly obstructed airways to the alveoli which they serve. This causes a progressively

greater proportion of the obligatory tidal volume to pass into the alveoli served by wider airways, with consequent overstretching of their walls and the development of higher elastic pressures. The lung appears more rigid. The time taken to fill a lung unit depends also on the distensibility or compliance of its alveoli, and it is the product of the compliance and resistance of the different lung units which determines their time constant, and the proportion of the ventilation they

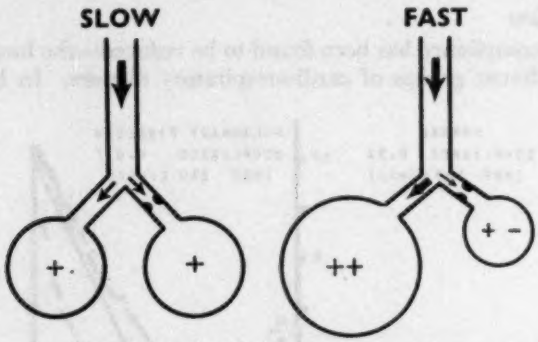

FIG. 7.—Schematic representation of alveoli (circles) and airways, showing influence of rate of inspiration on gas distribution and resultant elastic pressure change.

receive at different breathing rates (Otis *et al.*, 1956). The wonder is that the time constants are so even in the normal lung that the distribution of gas is almost unchanged at different rates.

Frictional Resistance

Lung tissue and airway resistance can be measured from the fatness of the loop. Thus at the same breathing rate the loop is much fatter in asthma, bronchitis and emphysema (Fig. 8), where there is a high airway resistance. This frictional resistance can be separated into its components—tissue and airflow resistances—by means of the body plethysmograph (Dubois *et al.*, 1956) (Fig. 9).

The Body Plethysmograph

The patient sits in an airtight box and pants through a flow meter. Simultaneous measurements of the airway resistance and the total volume of gas in the lungs can then be made. The measurement of airway resistance requires a simultaneous record of the alveolar pressure, which drives the gas through the airways, and the rate of airflow at the mouth.

$$\text{Airway resistance (cm. } H_2O\text{/L. per sec.)} = \frac{\text{Pressure difference between alveoli and mouth (atmospheric pressure)}}{\text{Rate of airflow}}$$

Alveolar pressure is equal to mouth pressure when the breathing tube is obstructed by a manometer near the mouth. The patient tries to pant against

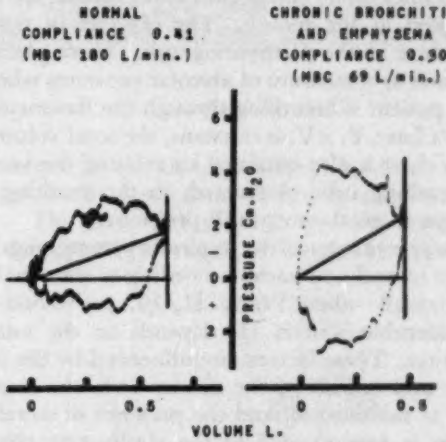

FIG. 8.—Pressure-volume recording of a patient with chronic bronchitis and emphysema contrasted with a recording from a normal subject breathing at the same rate.

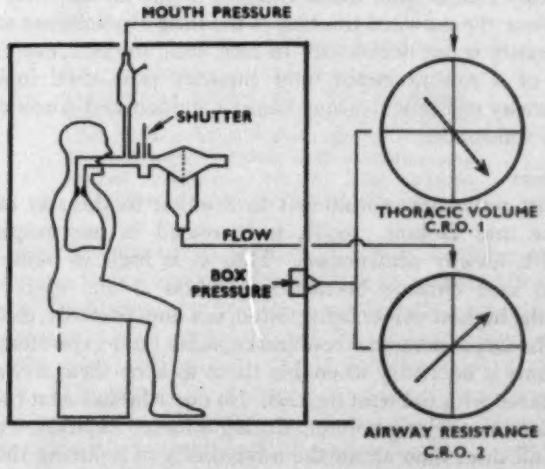

FIG. 9.—Body plethysmograph. Box pressure on horizontal axis of both oscilloscopes gives measure of thoracic volume when mouth pressure is on vertical axis and shutter is closed (C.R.O. 1), and airway resistance when airflow is on vertical axis with the shutter open (C.R.O. 2).

the obstruction, and alternately compresses and expands the gas in his chest at the pressures recorded at the mouth. The changes in volume cause small changes in the pressure in the plethysmograph. These plethysmograph pressures can then be used as a measure of alveolar pressures when the obstruction is released and the patient is breathing through the flowmeter.

Since, by Boyle's Law, P. $\times$ V. is constant, the total volume of compressible gas in the patient's chest is also obtained by relating the varying mouth pressures, with the breathing tube obstructed, to the resulting volume changes, measured as changes in plethysmograph pressure.

The normal airway resistance of the respiratory tract (lungs and nose) is about 3·5 cm. H_2O/L. per second and varies according to the nasal resistance. That of the lungs alone is small—about 1·0 cm. H_2O/L. per second—and remarkably constant over considerable periods. It depends on the number, length and patency of the airways. These factors are influenced by the pressure difference between the inside and outside of the airway wall, the muscular tone of the wall, the thickness of the mucosa, and the presence of secretions. At rest, the transmural pressure is proportional to the elastic retractive pressure of the lung and is directed outwards; the tonus of the airway wall, directed inwards, balances this force. At high lung volumes the elastic retractive pressure increases, so the bigger transmural pressure gradient dilates the airways, and the airway resistance falls. The airway resistance may, however, be sharply increased in normal subjects by the inhalation of bronchoconstrictor drugs or even of inert particles such as carbon or chalk dust (Dubois and Alcala, 1959). This presumably results from tonus changes in the airway wall or swelling of the mucosa, since the outward traction of the lung elastic tissue and transmural pressure difference is not decreased. In asthmatic subjects, exercise or even the performance of a routine rapid vital capacity test—used incidentally as a measure of airway resistance!—may cause a sudden and considerable increase in the airway resistance.

Disease Conditions

The airway resistance, considered in relation to the size of the patient's lungs (Briscoe and Dubois, 1958), is increased in any respiratory disease associated with airway obstruction. Thus it is high in acute (Dubois and Alcala, 1959) and chronic bronchitis (Dubois *et al.*, 1956), asthma, and emphysema, the highest values being found, not unexpectedly, during paroxysms of asthma. The large functional residual capacity (end-expiratory lung volume) in these patients is necessary to enable them to keep their airways sufficiently dilated to breathe with the least distress. No one who has seen the fall-off in the rate of airflow at lower lung volumes during a forced expiration can doubt this. Yet there is still discussion about the advisability of reducing the chest volume in patients with emphysema, as though the muscular disturbances necessitated by the maintenance of this inspiratory position were of primary importance.

Lung Tissue Resistance

Having measured the airway resistance, lung tissue resistance can be found by subtraction from the total frictional resistance measured with the œso-

phageal balloon. It is usually only about one-sixth of the total and may be increased in fibrosis and asthma (Marshall and Dubois, 1956).

Clinical Tests

Lung Compliance

All that is necessary for the measurement of lung compliance is a narrow bore water manometer and a polythene tube with a 15 cm. long balloon over the end (Fig. 10). The tube, with the balloon laxly deflated at atmospheric pressure, is passed through the nose into the œsophagus and the patient breathes

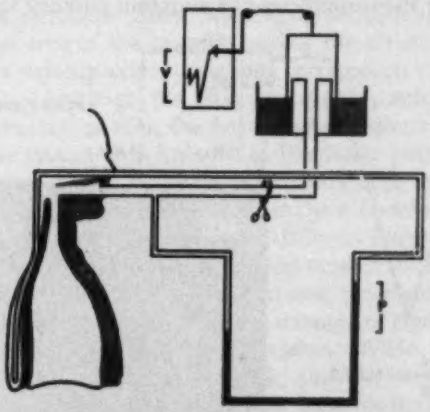

Fig. 10.—Simple method of measuring lung compliance. Narrow bore water manometer attached to œsophageal tube and breathing tube. After volume change, measured on the spirometer, clip is closed and transpulmonary pressure difference, at the lung volume, measured on the water manometer.

into a volume recorder, such as a spirometer. After expiring to the residual volume as a base line, he inspires and the clip is put on. The difference between mouth and œsophageal pressure (proportional to lung retractive pressure) is measured, and the process is repeated at different inspiratory volumes. The pressure difference is plotted against volume and the slope of this line is the lung compliance. It is important to ensure that the patient keeps his larynx open during the procedure. Accuracy is limited by the changes in balloon volume at large differential pressures (Petit and Milic-Emili, 1958).

Airway Resistance

The simplest and most useful measure of airway resistance is probably the forced expiratory volume record. This is the record of volume against time when the patient expires with maximum force, after a full inspiration, into a low inertia spirometer writing on a fast drum (Fig. 11). The volume expired

in unit time—usually one second—is measured, though it is the shape of the lower part of the curve which is most informative.

In normal subjects the maximum rate of expiration over the lower two-thirds of the vital capacity range is limited by the airway resistance (Hyatt *et al.*, 1958); extra expulsive effort merely narrows the airways and does not increase the airflow. This phenomenon is more marked in patients with obstructive airway disease, in whom extra expulsive effort may reduce the rate of air flow and lead to complete closure of some airways with associated trapping of gas. This is attributable to the fall in pressure, across an obstruction in the airway, at a high flow rate. The distending pressure in the airway mouthward of the obstruction is then insufficient to maintain patency against the compres-

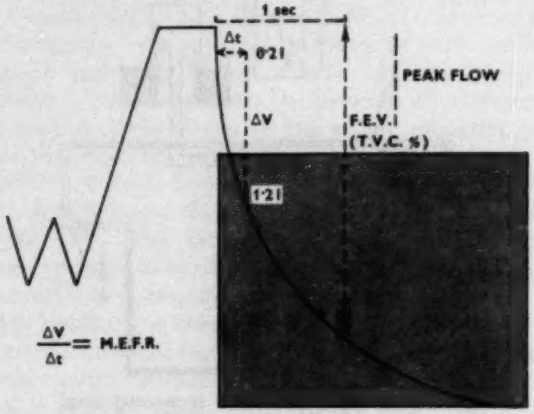

FIG. 11.—Force expiratory volume. The slope of the line in the shaded area is determined by the airway resistance (which may be increased by expiratory effort), while that above is mainly dependent on the effort made. M.E.F.R. = maximum expiratory flow rate.

sive efforts of the chest wall, and the airway collapses. The pursed lip breathing of an emphysematous patient maintains this distending force in the airways by slowing the rate of air flow.

The forced expiratory volume may be expressed as a percentage of the vital capacity (T.V.C.%) rather than just a volume, since people's lung volumes are related to their size. However, it is probably best expressed in relation to the predicted normal value (Miller *et al.*, 1959), since the vital capacity itself falls off considerably in severe obstructive airway disease. The addition of peak flow and maximum expiratory flow rate measurements seems superfluous. Maximum voluntary ventilation, in time with a metronome at 70 breaths per minute (Bernstein *et al.*, 1952), depends on other factors, such as familiarity with the test and the respiratory level, besides airway resistance; and there seems little point in " converting " the results of a forced expiratory volume to a figure for maximum breathing capacity. In fact it is doubtful if the effort required of a sick patient, in measuring maximum breathing capacity in

addition to the forced expiratory volume, is justified by the extra information gained. The forced expiratory volume has defects in that the previous volume history, rate of preceding inspiration (Capel and Smart, 1959), and the effort made have some influence; and the test itself may alter the airway resistance. It should be repeated after giving a broncho-dilator to assess the likely benefits of such treatment.

Work of Breathing

Mechanical Work

The pressure-volume diagram of the lung may also be used in measuring the work of breathing, or, more strictly, the work of lung movement, since chest wall factors are not included. Since work is, by definition, mean force times distance moved, the area of the triangle having the elastic line of the lung as hypotenuse, and the volume axis as base line, corresponds to the elastic work of inspiration (Fig. 3). Although the base line should, strictly speaking, be at atmospheric pressure, rather than the intrapleural pressure at the resting end-expiratory level, the system is in balance at this latter point, and the work of stretching the lung that far can be considered to have been done during development (Butler and Arnott, 1955). In fact it is the relaxation pressure curve of the chest wall which is the correct base line at different lung volumes (Campbell, 1958). The frictional work of inspiration is the area of the inspiratory bulge of the loop, and the total inspiratory work comprises the elastic triangle with this area. Expiratory frictional work falls in the triangle of elastic energy stored in inspiration, since expiration is normally passive. When it falls outside the triangle, this implies active expiratory work, and the area outside should be added to the inspiratory work to get the work done on the lungs in a complete breath. This work is usually about 0·5 Kg/m/minute (McIlroy *et al.*, 1954), but is increased in obstructive lung disease (increased frictional work) or in conditions where lung compliance is decreased (increased elastic work).

Oxygen Cost of Breathing

The total mechanical work performed by the chest muscles in moving the chest wall as well as the lungs is difficult to measure; the pressure-volume diagram of the total respiratory system obtained with the cabinet respirator is fallacious in that no one can relax completely. However, the oxygen cost of an increase in ventilation can be fairly easily estimated (Hyatt *et al.*, 1958). The increase in ventilation may be obtained by adding various dead spaces to the breathing tube of a B.M.R. machine which is used to measure the resulting increase in oxygen uptake. Such studies have shown that equal increments in ventilation cause greater increases in oxygen uptake as the total ventilation is increased. In the normal range, values of about 0·5 to 1 ml. oxygen per litre of ventilation are found, indicating an efficiency of about 7 per cent.

Summary

(1) The pressures developed at the mouth at different chest volumes, when relaxing against an obstruction, characterise the elastic properties of the lung

and chest wall. During movement additional pressures are necessary to overcome frictional forces due to the frictional resistance of the lungs and chest wall and the resistance to airflow in the lungs. The curve of these pressure-volume relationships forms a closed loop during a complete breath, the pressure-volume diagram.

(2) The pressure-volume diagram of the lungs alone can be obtained by relating intrapleural (measured as œsophageal) pressure to lung volume during breathing. The static pressure-volume relationships of the lung show an increased rigidity (reduced compliance) in heart failure, pulmonary infiltrations, obstructive airway disease (due to fall in ventilated space with increasing rates of breathing), and in conditions where lung expansion is restricted. The frictional "fatness" of the diagram is greater in obstructive airway disease with high airway resistance.

(3) Clinically, lung compliance may be measured with an œsophageal balloon, water manometer and spirometer. Airway resistance is assessed from the forced expiratory volume record.

(4) The mechanical work of breathing may be measured from the pressure-volume diagram and the oxygen cost of breathing from the increased oxygen uptake associated with hyperventilation.

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THE EVALUATION OF ABNORMALITIES OF THE BLOOD GASES

By Peter Harris

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Unfortunately, the composition of peripheral venous blood is of no help in the investigation of respiratory diseases. One is interested primarily in the state of the blood as it leaves the lungs, and the nearest approach to this is the arterial blood. This contribution is, therefore, concerned entirely with the gases in arterial blood.

The Composition of Arterial Blood

The *oxygen content* of blood is the volume of oxygen dissolved in 100 volumes of blood. A representative normal value for arterial blood would be 19·8 vols. per cent. This volume of oxygen is mainly present in combination with hæmoglobin, but a small quantity exists in simple solution. The *oxygen saturation* is the percentage of the total hæmoglobin which exists in the oxygenated form. One gram of hæmoglobin can combine with 1·34 ml. of oxygen, so that 100 per cent. saturation represents 20·1 vols. per cent. of oxygen when the hæmoglobin is 15 g./100 ml. Since the normal arterial saturation is about 97 per cent. the quantity of oxygen in combination with hæmoglobin would be $97/100 \times 20{\cdot}1 = 19{\cdot}5$ vols. per cent. The remaining 0·3 vol. per cent. of oxygen is present in physical solution. The partial pressure of this dissolved oxygen (P_{O_2}) is normally about 95 mm. Hg in arterial blood and 0·1 vol. per cent. of oxygen dissolves for every 30 mm. Hg rise in P_{O_2}. The *oxygen capacity* is the content of oxygen existing when blood is equilibrated with room air. In this condition the blood is 100 per cent. saturated and contains 0·5 vol. per cent. of oxygen in solution, corresponding to a P_{O_2} of about 150 mm. Hg. If the hæmoglobin is 15 g./100 ml., the oxygen capacity will be $20{\cdot}1 + 0{\cdot}5 = 20{\cdot}6$ vols. per cent. provided that all the hæmoglobin is normal. The relationship between the oxygen content and the P_{O_2} has the well-known sigmoid shape dictated by the oxygen dissociation curve of hæmoglobin.

Carbon dioxide in blood is present partly in solution, partly as bicarbonate and partly in combination with hæmoglobin. Normal blood has a partial pressure of carbon dioxide (P_{CO_2}) of about 40 mm. Hg. The shape of the carbon dioxide dissociation curve is less complex than that for oxygen and has a steeper slope within the physiological range.

Carbon Dioxide and the Acidity of the Plasma

Carbon dioxide plays an important part in the regulation of the acidity of the plasma. When this gas dissolves in water it forms carbonic acid:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$

Carbonic acid then ionises to form hydrogen ions and bicarbonate ions:

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Since this is a highly reversible reaction, it may be expressed in the form of mass action equation:

$$k[H_2CO_3] \rightleftharpoons [H^+] \times [HCO_3^-]$$

which may be rearranged:

$$[H^+] = k.\ \frac{[H_2CO_3]}{[HCO_3^-]}$$

Thus the concentration of hydrogen ions, which determines the acidity of the plasma, is directly proportional to the ratio of the concentrations of carbonic acid and bicarbonate, k being an equilibrium constant.

If carbon dioxide is acutely retained in the body by under-ventilation of the alveoli, there is an increase in the proportion of carbonic acid to bicarbonate in the plasma and the plasma becomes more acid. In this condition of respiratory acidosis the carbon dioxide content of the blood is therefore abnormally high, whereas it will be remembered that in metabolic acidosis the carbon dioxide content of the plasma is low. With chronic retention of carbon dioxide the kidneys can retain base so that plasma bicarbonate increases and the ratio of carbonic acid to bicarbonate is restored. In this way the acidity of the plasma is returned towards normal.

The Composition of Alveolar Air

The meaning of abnormalities of the arterial blood gases can only be interpreted in relation to the partial pressures of these gases in the alveoli. One can arrive at the alveolar P_{CO_2} very easily because this can be assumed to be the same as the arterial P_{CO_2}. This assumption cannot lead to much error, since carbon dioxide is so highly transmissible and since the arterio-venous difference in P_{CO_2} is in any case only about 6 mm. Hg. Measurement of the alveolar P_{O_2} presents a greater problem and necessitates the analysis of the expired air. It is then calculated from the approximate formula:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R}$$

$$= P_{I_{O_2}} - \frac{P_{a_{CO_2}}}{R}$$

Where $P_{A_{O_2}}$ is the alveolar P_{O_2}; $P_{I_{O_2}}$ is the known partial pressure of oxygen in the inspired air; $P_{A_{CO_2}}$ is the alveolar P_{CO_2} which is taken as being equal to $P_{a_{CO_2}}$, the arterial P_{CO_2}; and R is the respiratory exchange ratio calculated from the analysis of the mixed expired air.

There are three major circumstances which lead to disturbances of gaseous exchange in the lung. These are: an abnormal total alveolar ventilation; an uneven distribution of the ventilation: perfusion ratio; and an impairment of diffusion.

The Effects of an Abnormal Total Alveolar Ventilation

The tissues of the body consume about 250 ml. of oxygen per minute and produce about 200 ml. of carbon dioxide. In a steady state, these are also the rates of exchange of gases in the lungs. Whatever the rate of alveolar ventilation, these volumes of gases have still to be exchanged each minute. If alveolar ventilation is decreased, carbon dioxide still continues to pour into the alveoli and oxygen still continues to be extracted from them at the same rate. There is, therefore, a raising of the alveolar P_{CO_2} and a lowering of the alveolar P_{O_2}. These changes are reflected in the arterial blood. There the rise in P_{CO_2} leads to a rise in the carbon dioxide content. A small fall in P_{O_2} may not lead to much reduction in the oxygen content, but as soon as the steep portion of the dissociation curve is reached the oxygen content and saturation fall rapidly. The net effects of substantial underventilation on the arterial blood are, therefore, a rise in P_{CO_2} and carbon dioxide content and a fall in P_{O_2} and oxygen content.

Over-ventilation of the alveoli has the reverse effect on the composition of the alveolar air. The P_{CO_2} falls and the P_{O_2} rises. Again these changes are reflected in the arterial blood. But, although the fall in arterial P_{CO_2} is associated with a fall in carbon dioxide content, the rise in P_{O_2} does not lead to much increase in the content of oxygen. This is because the change in P_{O_2} occurs on the plateau of the oxygen dissociation curve. In other words, the blood leaving the alveoli is already 98 per cent. saturated with oxygen under normal conditions, and over-ventilation can, therefore, do very little to increase this.

The Effects of an Uneven Distribution of Ventilation : Perfusion Ratios

The ratio of alveolar ventilation to capillary perfusion is usually around 4 : 5. Even in normal lungs, this ratio varies slightly from alveolus to alveolus. In disease, and characteristically in emphysema, the variation in the ventilation : perfusion ratio throughout the lung can become very wide and leads to arterial anoxæmia.

To illustrate how this occurs, we shall consider the lung to be divided into two portions, one with a high ventilation : perfusion ratio and the other with a low ventilation : perfusion ratio. The alveolar P_{O_2} of the portion with a high ratio will naturally be higher than that of the portion with a low ratio. Since we shall assume that complete equilibration occurs between the alveolar air and the end-capillary blood, the P_{O_2} of the blood leaving the portion with a high ventilation : perfusion ratio will also be higher than the P_{O_2} of the blood leaving the portion with a low ratio.

The value for the mixed alveolar P_{O_2} is mainly influenced by the large contribution of alveolar air from the portion with a high ventilation : perfusion ratio. The value for the mixed end-capillary P_{O_2} is, on the other hand, mainly influenced by the large contribution of blood from the portion with the low ventilation : perfusion ratio. The value for mixed alveolar P_{O_2} comes, therefore, to be higher than that for mixed end-capillary P_{O_2}.

Part of the difference in P_{O_2} is due to the influence of the shape of the

oxygen dissociation curve. Although the blood leaving the portion with a low ventilation : perfusion ratio has a low content of oxygen, the oxygen content of the blood leaving the portion with a high ventilation : perfusion ratio is not raised to the same extent above normal. This is again due to the fact that the raised P_{O_2} in the well-ventilated portion lies on the plateau of the oxygen dissociation curve. Thus some diminution of the mixed end-capillary P_{O_2} would arise even if the distribution of blood flow to each portion of the lung were equal.

The arterio-venous difference in P_{O_2} across the lungs is 50-60 mm. Hg. The arterio-venous difference in P_{CO_2} is only about 6 mm. Hg. Hence an unevenness of ventilation : perfusion can cause only a slight rise in the arterial P_{CO_2}, and this slight rise may be easily corrected by an increase in the total ventilation due to stimulation of the respiratory centre.

The Effects of an Impaired Diffusing Capacity

This subject is dealt with in greater detail elsewhere in the symposium. The effect of any impairment of the diffusing capacity is to impede the passage of oxygen from the alveoli to the capillaries. The passage of carbon dioxide is not substantially affected because this gas is so highly transmissible. The net effect of an impaired diffusing capacity is, therefore, to prevent the equilibration of oxygen between the alveolus and the capillary, and the blood leaves the lungs with a lower P_{O_2} than the alveolar P_{O_2}. The arterial blood, therefore, shows a fall in P_{O_2}. There should be no change in arterial P_{CO_2}, but frequently this is low because patients with this disorder tend to over-ventilate.

Abnormalities of the Blood Gases in Emphysema

We may, in summary, retrace our steps over these theoretical considerations by applying them to the physiological disturbances which accompany emphysema. All three major abnormalities occur in this disease in varying degrees —alveolar under-ventilation, uneven ventilation : perfusion, and to a slight extent a decreased diffusing capacity. The lack of uniformity of ventilation : perfusion which is so readily understandable from the ventilatory side causes by itself a certain degree of arterial anoxæmia and this may be increased a little by some impairment of the diffusing capacity. Early in the course of the disease, the very slight rise in arterial P_{CO_2} caused by uneven ventilation : perfusion can be rectified by increasing the total ventilation and anoxæmia is the sole abnormality of the blood. But, as the disease progresses, the airway resistance increases and the ventilatory capacity becomes more and more limited. So that eventually the effects of alveolar under-ventilation are superadded and carbon dioxide retention occurs. At first the retention of carbon dioxide is usually episodic, accompanying attacks of bronchial infection. Such acute retention of carbon dioxide raises the ratio of carbonic acid to bicarbonate in the plasma and causes acidosis. Eventually the retention of carbon dioxide becomes permanent. In these circumstances the kidneys have time to conserve base so that the concentration of bicarbonate also rises. This restores the ratio of carbonic acid to bicarbonate and corrects the acidity of the plasma.

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THE ESTABLISHMENT OF A LABORATORY FOR THE ASSESSMENT OF PULMONARY FUNCTION

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The various aspects of the function of the lungs have been discussed individually, and different ways in which this function can be tested have been mentioned. It is now necessary to consider the place of these tests in clinical practice and to decide which of them should be available in a laboratory for the testing of pulmonary function. It is reasonable to enquire, in the first place, what is the practical value of the testing of pulmonary function by these methods in clinical practice. There is no doubt that the application of these techniques to patients with various diseases has thrown much light on the disturbances of function which are present in these conditions. It is only as a result of such investigations in the past that we now understand the different functional disturbances in, for instance, emphysema or in diffuse pulmonary sarcoidosis. And yet, the physician who begins to use such tests in individual patients in the hope of obtaining results of diagnostic importance is, in general, likely to be disappointed. This is not to deny their diagnostic value in a small number of patients, or their considerable value as a guide in certain forms of treatment and in the assessment of the progress of a disease or the results of treatment. Particularly in the latter circumstance the tests have an invaluable place in demonstrating objective changes in the functional state of the lungs as opposed to the purely morphological change indicated by radiological examination.

In order to use the tests of pulmonary function efficiently it is essential that the investigator who is making the measurements should have a clear understanding of their physiological background and of what each test is measuring. Furthermore, it is desirable that the tests should be carried out by someone having full knowledge of the clinical features of the patient, preferably a clinician concerned with his care. The value of the tests is much diminished if performed as a routine service by a laboratory worker who has only brief contact with the patient and who knows only the bare details of the clinical problem.

If these conditions are accepted it is evident that it is of great value to the clinician himself if he undertakes this type of study on his patients. He finds it essential to study the relevant physiological mechanisms and as a result he comes to think about his patients in terms of disordered function. This necessary consideration of a different aspect of the disease must inevitably result in a better and more complete understanding of disease processes. Such an understanding cannot be obtained so well or so quickly by any other means than by the personal application of these procedures to patients as they present in clinical practice. After applying the tests to a large number of patients, the

investigator comes to recognise the pattern of functional disorder without the need to apply tests in all patients. The experience he has achieved enables him to use the tests more sparingly, and later still he will find them necessary in only a selected few patients presenting some more obscure disorder or problem in treatment. It is clear that the testing of pulmonary function can be of considerable direct value to the patient, but in relatively few instances. More importantly, however, all patients benefit indirectly because the clinical problems they present will be handled better by the physician who has achieved an understanding of their disordered functional state as a result of his experience of applying such tests to similar patients in the past.

The question next arises as to how a laboratory for the assessment of pulmonary function should be equipped. Many tests have been mentioned in this Symposium and although, ideally perhaps, the laboratory should be able to apply all of them when needed, it should be noted that several tests may measure essentially the same function. Since there are a number of aspects of the lung's function to be investigated, there can be no question of any test being the " best " or even the " most useful." Nevertheless, it is possible to select a limited number of tests and the necessary equipment which will enable an adequate investigation of most of the clinical problems likely to be encountered. In making a selection from the available tests, several factors have to be considered, although the final choice is to some extent a personal one. Among the relevant factors are the following:

(*a*) Simplicity and speed in performance of the test is desirable. A test which can be performed rapidly is an advantage to the patient and to the doctor. It also makes it possible to make several observations, the resulting mean value being statistically sounder than a single maximum value. The procedure should also be simple, easily explained to the patient, and should not involve unnecessarily complicated respiratory manœuvres.

(*b*) The test should depend as little as possible on the patient's active co-operation. The patient may fail to co-operate through inability to understand what is asked of him, because he is unable to concentrate on the test or because he is afraid or not prepared to exert himself fully. A test which avoids these difficulties has obvious advantages.

(*c*) The test should preferably use apparatus which is inexpensive and easy to maintain. This is an obvious qualification in a routine test, but it should not be forgotten that a relatively expensive piece of equipment may represent a true economy in expenditure when the time saving is taken into account.

It is clearly not always possible to reconcile all of these factors but, taking them into consideration, it is suggested that the following basic equipment will permit a full assessment of most aspects of pulmonary function.

1. *Spirometer.* The most suitable type is one made with the design features described by Bernstein *et al.* (1952), which ensure a low inertia and minimise the resonance distortions which are liable to occur when recording rapid oscillations of the spirometer bell. The capacity of the bell should be at least 6 litres and a kymograph with two speeds is required, the convenient paper speeds being 2 mm./sec. and 20 mm./sec. The former speed is suitable for

recording the vital capacity and other static lung volumes and also the maximum breathing capacity, while the latter permits the recording of forced expiratory and inspiratory tracings. From such a tracing the various indices of the maximum expiratory flow rate can be measured, such as the maximum mid-expiratory flow rate (Leuallen and Fowler, 1955) and the percentage of the vital capacity expired in one second.

2. *Peak Flow Meter* (Wright and McKerrow, 1959). Although this instrument has not been in use very long, and therefore its clinical value has not been fully investigated, it seems likely to be very useful as a simple portable apparatus for the determination of the degree of airways obstruction.

3. *Equipment for Measuring Pulmonary Ventilation and Analysing Expired Gas.* The simplest way of collecting expired gas is by the use of a lightweight Douglas bag with the necessary respiratory valve. The volume collected is then measured by passing it through a dry gas meter which, although a little less accurate than a wet meter, is more sturdy and simpler to use. Expired gas is stored in mercury filled sampling tubes and analysis is most easily made in the Scholander (1947) micro-gas analysis apparatus. Using this apparatus and a large anæsthesia bag, it is possible to estimate the mixed venous blood carbon dioxide tension by the rebreathing method which is described elsewhere in the subsequent discussion.

4. *Equipment for the Sampling and Analysis of Arterial Blood.* Puncture of the brachial artery, using an indwelling needle, is performed under local anæsthesia. Blood is drawn into a lightly oiled, all-glass syringe, the dead space of which is filled with a solution of heparin. A small drop of mercury is drawn into the syringe, which is sealed with a needle hub. It is best to analyse the blood at once, but if this is not possible it should be kept well mixed.

The percentage oxygen saturation of the blood can be estimated by use of the Van Slyke apparatus, but this is time consuming and it is not practicable when more than two or three samples have to be analysed. It is, therefore, preferable to use a spectrophotometric method, of which several have been described (Wade *et al.*, 1953; Roddie *et al.*, 1956). At the present time the arterial carbon dioxide tension is most readily determined by the use of the principle employed by Astrup (1956) in which the *p*H of anaerobically separated plasma is measured before and after equilibration with gas mixtures of known carbon dioxide content. The method, which also estimates the original plasma *p*H, need not of necessity employ the equipment as described by Astrup, the essential requirements being a glass electrode and means for measuring its output and vessels into which the plasma is introduced and in which it may be equilibrated.

Additions to this list could easily be made; for instance, a test for uneven distribution of inspired air might be considered to be almost essential. Nevertheless, most patients can be adequately investigated with this equipment. The decision as to which of the tests to apply in a particular patient will depend upon an understanding of the purpose of each test, and on a knowledge of the clinical features of the patient. In most patients spirometry will be the first procedure, the static lung volumes and a fast expiratory tracing being recorded.

This may, for instance, give confirmatory evidence of the airway obstruction characteristic of emphysema, and repetition after the use of a bronchodilator aerosol will demonstrate the extent to which this obstruction is reversible. It is then necessary to determine how severely the process is interfering with pulmonary gas exchange, and this is studied by sampling and analysing arterial blood sampled at rest and during or after a few minutes' exercise. If, on the other hand, spirometry suggested the presence of a restrictive limitation of the lung volumes, the possibility of a diffuse pulmonary infiltration with the alveolo-capillary block syndrome would be considered. Under these circumstances hyperventilation might be demonstrated at rest with a low arterial carbon dioxide tension and an arterial oxygen saturation which, although normal at rest, became definitely abnormal during exercise.

This attempt to describe the purpose of a laboratory for testing pulmonary function and the way in which it could be established represents a personal view, with which some will disagree. In particular the choice of equipment and the selection of tests to be used is without doubt open to criticism, many other selections being possible. The object of this contribution will have been achieved if it promotes thought and discussion.

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THE REBREATHING METHOD OF ESTIMATING ARTERIAL AND MIXED VENOUS CO_2 TENSION

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The arterial CO_2 tension (P_{CO_2}) depends on the balance between metabolic CO_2 production and alveolar ventilation.

$$P_{CO_2} \propto \frac{CO_2 \text{ production}}{\text{alveolar ventilation}}$$

The interpretation of changes in P_{CO_2} is so unequivocal and clinically significant that the measurement would be as commonplace in practice as the blood urea, were it not for technical difficulties.

Collier (1956) showed that the P_{CO_2} of mixed venous blood can be estimated quickly and simply by the use of a continuous rapid CO_2 analyser. The method consists of having the subject rebreathe a CO_2-air or CO_2-O_2 mixture from a small bag while measuring the CO_2 concentration at the mouth (Fig. 1). If the correct initial CO_2 concentration is used (Fig. 1B) the mixture of the air in the bag and lungs comes to have a P_{CO_2} close to that of the mixed venous blood entering the lungs in the pulmonary arteries. This blood then takes up or gives off CO_2 until its P_{CO_2} is identical with that in the bag and lungs. There is now an equilibrium until blood, which has left the lungs unable to give off CO_2, returns from the tissues with a higher P_{CO_2}. During the equilibrium air passes backwards and forwards between the bag and the lungs without changing P_{CO_2}, producing a "plateau" in the record (Fig. 1B, between 8 and 13 secs.). This plateau is the mixed venous P_{CO_2}. The time available for these equilibria to be attained is limited by recirculation to less than 20 seconds. If a plateau is not obtained other CO_2 mixtures are tried until a plateau is found.

The mixed venous-arterial P_{CO_2} difference is approximately 6 mm. Hg and varies little over a wide range of cardiac output in the resting subject.

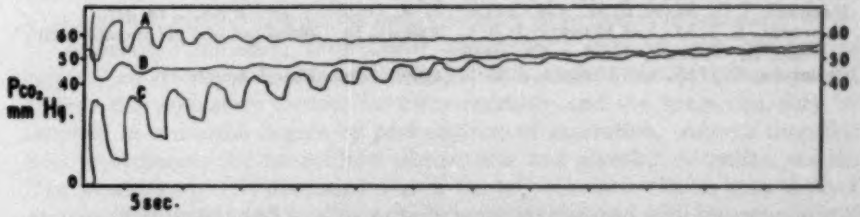

Fig. 1.—Records taken from a normal subject at rest rebreathing from a 2 l. bag. *A*: initial P_{CO_2} in bag 95 mm. Hg. *B*: initial P_{CO_2} 54 mm. Hg. *C*: initial P_{CO_2} 0 mm. Hg.

Note (1) The similar final P_{CO_2} values in all records, (2) the "plateau" in record *B* between 8-13 seconds after the beginning. (Campbell and Howell, 1960a; reproduced by kind permission.)

Hackney *et al.* (1958), in fact, found that the arbitrary subtraction of 6 mm. Hg from the mixed venous P_{CO_2} estimated the arterial P_{CO_2} with an accuracy of ±3 mm. Hg.

Campbell and Howell (1960a) noted that the rebreathing of any CO_2 mixture from 0 to 100 mm. Hg for 1-1½ minutes produced a P_{CO_2} of the same order as that required to obtain a plateau (Fig. 1A, C). In fact a plateau could be obtained by (1) rebreathing any O_2, air or CO_2 mixture with a P_{CO_2} of 0-100 mm. Hg for 1½ minutes, (2) waiting 2-3 minutes, (3) rebreathing from the same bag. They further noted that analysis of the bag during (3) above at 20 seconds gave a P_{CO_2} insignificantly higher than that of the plateau. The necessity for a rapid CO_2 analyser was thus removed.

These findings were amplified and the accuracy was checked in a series of patients with a wide range of abnormal arterial CO_2 tensions (Campbell and Howell, 1960b). The accuracy found was again ±3 mm. Hg.

Our recommended procedure for estimating mixed venous P_{CO_2} is as follows:

(1) Fill a bag with 1½-2 l. of O_2.
(2) Rebreathe for 90 seconds. If the tidal volume is small, partly empty the bag (without disconnecting it from the patient) until the bag is approximately half emptied by each inspiration.
(3) Wait 2 minutes.
(4) Rebreathe for 20 seconds or 5 breaths (whichever is longer).
(5) Analyse by any convenient method and the P_{CO_2} of the bag can be taken to equal mixed venous P_{CO_2}.

Comparison with arterial P_{CO_2} measurements can be made by subtracting 6 mm. Hg. We, however, prefer to use the observed mixed venous value for several reasons (Campbell and Howell, 1960a).

This description has necessarily been brief. As the problems of the method are essentially physiological rather than technical, reference should be made to the fuller accounts of the principles involved.

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Functional Aspects of Pulmonary Disease

THE DISORDERED PHYSIOLOGY OF OBSTRUCTIVE BRONCHIAL DISEASE

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The disordered physiology of obstructive bronchial disease can conveniently be considered under two main heads, firstly, when many or most of the bronchioles are obstructed, as in emphysema associated with chronic bronchitis or asthma, and secondly, when there is obstruction of a single large bronchus, as in carcinoma of the bronchus or post-operative atelectasis.

1. Emphysema due to Chronic Bronchitis or Asthma

Except in the rare cases of primary emphysema of which the cause is quite unknown, widespread bronchiolar obstruction is the basic fault from which emphysema and all its sequelæ develop. In chronic bronchitis inflammatory œdema and fibrosis of bronchiolar walls and endobronchiolar mucus are the pathological processes responsible for narrowing their lumina, while in asthma it is plugging of the bronchioles by mucus, thickening of the basement membrane, œdema and eosinophilic infiltration of the whole bronchiolar wall, and sometimes detachment of the superficial ciliated epithelium, that cause the obstruction.

Normally the diameter of a bronchiole in inspiration is about twice its diameter in expiration. This is due to the fact that the whole bronchial tree participates in the general increase of intrathoracic volume during inspiration and its overall decrease during expiration. If, therefore, the diameter of a given bronchiole were normally 5 mm. in inspiration and 2·5 mm. in expiration and bronchiolar narrowing as a result of bronchitis reduced its diameter by 1 mm. in inspiration, the cross-sectional area of the bronchiole would be 12·57 sq. mm. instead of 19·64 sq. mm. (*i.e.* 64 per cent. of normal) and in expiration 1·77 sq. mm. instead of 4·91 sq. mm. (*i.e.* only 36 per cent. of normal).

Although, therefore, bronchiolar obstruction impedes the passage of inspired air from the trachea and main bronchi to the alveoli, it obstructs and retards the expiratory airflow far more seriously and the lungs can only be emptied to a normal degree by prolongation of expiration. After a time this fails to overcome the bronchiolar obstruction and alveolar distension results. The pressure of such distended alveoli on adjacent bronchioles may further narrow their lumen and lead to a check valve mechanism with increased distal trapping of air. In due course the prolonged alveolar distension results in rupture of alveolar septa. Paroxysms of coughing which cause a marked temporary increase in intra-alveolar pressure are an important aggravating influence in this respect. The ruptured alveolar septa undergo fibrosis and

adjacent alveoli become converted into large air spaces. The long-standing increase in expiratory intra-alveolar pressure, the alveolar distension and the rupture of the alveolar septa lead to a progressive decrease in lung elasticity and tension and this further impairs the capacity of the lungs to empty themselves in a normal manner during expiration. These defects result in profound and increasing ventilatory insufficiency which is, in the earlier stages of emphysema, the sole functional defect and in advanced cases still the dominant influence. The pathological processes above outlined and the degree of ventilatory insufficiency that ensues therefrom are accurately mirrored by the abnormalities in the various measurements of ventilatory function. Firstly, in the lung volume measurements, the obstruction to expiratory air flow is shown

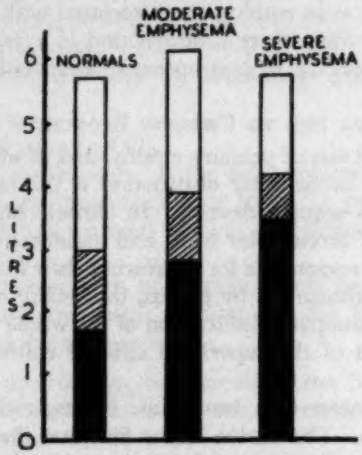

FIG. 1.—Lung volume of normal subjects compared with that of emphysematous patients. Residual volume—black. Expiratory reserve volume—hatched. Inspiratory capacity—white.

in the marked slowing of expiration on the spirogram, and although the vital capacity is usually reduced the maximum expiratory flow rate and timed vital capacity measurements focus the defect more clearly, the emphysematous patient being unable to exhale 80 per cent. of the total vital capacity in the first second as can normal subjects. The high inspiratory position of the chest and the increased volume of air in the lungs at the end of a normal expiration are shown by the elevation of the resting respiratory level, the inspiratory capacity comprising a lower proportion and the expiratory reserve volume a higher proportion of the total vital capacity than they normally do. The alveolar distension produces an increase in the residual volume—the amount of air remaining in the lungs at the end of maximal expiration. This increase is both absolute and relative—that is, when expressed as a ratio of the total lung volume—and this latter percentage is a good index of the degree of ventilatory

insufficiency (Fig. 1). The defective ventilation is, however, more accurately assessed by the maximum breathing capacity than it is by lung volume measurements. The maximum breathing capacity is a more dynamic test and depends on the ability of the subject to develop high airflow velocities, a capacity always markedly reduced in emphysematous patients. It reflects the diminution in exercise tolerance which in emphysema is the most striking symptom, and grossly subnormal values may be found in patients in whom the lung volume measurements are not greatly altered. The high inspiratory position at which the maximum breathing capacity is performed, again, reflects the elevation of the resting respiratory level and the increased volume of air remaining in the lungs at the end of expiration. Diminution in the maximum breathing capacity and increase in the resting minute ventilation both contribute to a reduction in the breathing reserve, and when this falls to 70 per cent. or less severe exertional dyspnœa is present. The degree of bronchial obstruction and the inability to produce high airflow velocities are well shown by the air velocity index, which contrasts the reduction in maximum breathing capacity with the reduction in vital capacity. In normal subjects this is, of course, unity, but in emphysematous patients an index of 0·5 is not uncommon. The bronchiolar obstruction, alveolar distension, destruction of alveolar septa and loss of lung elasticity lead to defective alveolar mixing of the inspired air with that remaining in the lungs at the end of the previous expiration. The normal index of intra-pulmonary mixing is not more than 2·5 per cent. of nitrogen, but in emphysema this may be increased four- or five-fold. The main function of ventilation is, of course, to provide a gradient of oxygen sloping from the alveoli to the pulmonary capillary blood, and a gradient of carbon dioxide in the reverse direction. These gradients become increasingly difficult to maintain as ventilatory insufficiency advances and intra-pulmonary mixing becomes progressively impaired. Oxygen diffuses into the pulmonary capillary blood much less readily than does carbon dioxide from it, and anoxia is, therefore, the first evidence of impairment of blood gas exchange, but for a long time a compensatory increase in minute ventilation and the fact that some parts of the lung are still relatively normal suffice to maintain an overall ventilation sufficient to prevent anoxia from developing, and at this stage the hyperventilation results in increased washing out of carbon dioxide from the pulmonary capillary blood and subnormal arterial carbon dioxide tensions.

In asthmatic subjects and in bronchitics with superadded bronchospasm, broncho-dilator drugs will reduce the degree of bronchiolar obstruction and ventilatory insufficiency and lessen all the abnormalities in the various tests of ventilatory function.

The disordered physiology of emphysema is more easily understood by dividing it into three stages; first, the stage of pure ventilatory insufficiency; second, when alveolo-respiratory insufficiency becomes added to ventilatory insufficiency; and, third, the stage of chronic cor pulmonale. So far pure ventilatory insufficiency has been described. At this stage (stage 1) the symptoms will be cough and wheezing with tenacious mucoid sputum and undue dyspnœa on exertion. The physical signs will be those of emphysema with or

without bronchospasm. Cyanosis will be absent. The chest radiograph will be that of emphysema with a small heart shadow, and the electrocardiogram will be normal. However, as ventilatory insufficiency steadily increases the time arrives when hyperventilation can no longer compensate it and, in consequence, the alveolar air throughout the lung comes to contain too little oxygen and too much carbon dioxide. This of itself prevents the maintenance of normal exchange of oxygen and carbon dioxide between the alveolar air and the pulmonary capillary blood, but at the same time other equally important factors are operating in the same direction. Firstly, the rupture and fibrosis of alveolar septa and the replacement of many alveoli by large air spaces leads to an enormous reduction in the surface area available for blood gas exchange; and, secondly, alveoli which may still be reasonably well ventilated may be underperfused with pulmonary capillary blood and well-perfused alveoli may be underventilated. To ventilatory insufficiency there is, therefore, now added alveolo-respiratory insufficiency. As has already been stated, carbon dioxide diffuses out of the pulmonary capillary blood much more readily than does oxygen into it, and the first manifestation of alveolo-respiratory insufficiency is anoxia. Initially it is still possible to maintain normal oxygen saturation of the arterial blood at rest, and desaturation is only evident when the oxygen requirement is increased by exercise, but in due course anoxia is present at all times, the arterial oxygen saturation falling to lower levels on exercise. Ultimately carbon dioxide retention occurs and the blood *p*H falls.

At this stage (stage 2, ventilatory insufficiency plus alveolo-respiratory insufficiency) cyanosis becomes added to the clinical features already described and other symptoms and signs attributable to carbon dioxide retention may become manifest. These comprise headache, sweating, weakness, lassitude, drowsiness, confusion, irritability, muscle twitchings, myoclonic jerks, delirium, mania and coma. These features appear to be mainly due to the decompensated respiratory acidosis which has the effect of lowering cerebral oxygen consumption, and when this falls to levels below 2·1 c.c. per 100 g. of brain tissue per minute unconsciousness invariably occurs (Kety *et al.*, 1948). A depression of the arterial *p*H to 7·2 produces mental disturbance and at levels of 7·1 coma is usual (Westlake *et al.*, 1955). Extreme hypercapnia may however cause profound mental disturbances and depression of consciousness even when the arterial *p*H is at higher levels and both factors doubtless play their part, though acidæmia seems to be the more important of the two. Other mechanisms besides the direct effect of acidæmia and hypercapnia are, however, involved. Hypercapnia leads to an increase in cerebral blood flow, a rise in intracranial pressure and sometimes papilloedema, and the high cerebro-spinal fluid pressure tends to decrease cerebral oxygen consumption. Certainly the muscle twitchings and myoclonic jerks may be caused by anoxia alone, although elevation of the carbon dioxide tension is a more important influence. Although the carbon dioxide intoxication syndrome is seen in untreated cases of severe emphysema it is commonly precipitated by the administration of morphine or barbiturates, both of which decrease ventilation and thereby increase carbon dioxide retention, or by the indiscriminate use of oxygen. The danger of oxygen

therapy arises from the fact that in hypercarbia the medullary respiratory centre becomes insensitive to the increased carbon dioxide content of the blood and respiration appears to be maintained by the stimulus of the low arterial oxygen tension on the chemoreceptors of the carotid and aortic bodies. Elevation of the arterial oxygen content by oxygen administration may remove this stimulus and lead to hypoventilation or even apnœa, with resultant precipitate further increase in carbon dioxide retention and the degree of decompensated respiratory acidosis.

The factors leading to the development of cor pulmonale (stage 3) are multiple and are summarised in Fig. 2. The progressive diminution in the pulmonary capillary bed which results from the rupture and fibrosis of alveolar walls makes it increasingly difficult for the right ventricle to propel blood

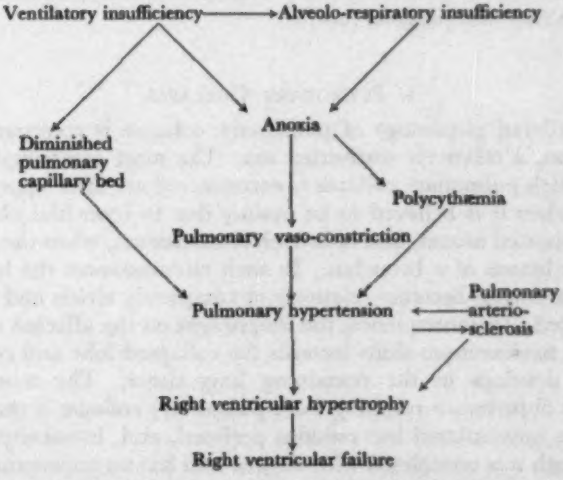

FIG. 2.—Factors leading to the development of cor pulmonale.

through the pulmonary circulation, and this difficulty is augmented by the anoxia which causes pulmonary vaso-constriction and by a rise in cardiac output which develops in an endeavour to compensate for the structural and functional abnormalities that have taken place in the lungs. An additional compensatory development which sometimes occurs is polycythæmia, and although this increases the oxygen carrying capacity of the blood its higher viscosity adds to the load on the right ventricle. Right ventricular hypertrophy and pulmonary hypertension therefore develop. The latter is readily confirmed by cardiac catheterisation, the electrocardiogram often shows evidence of right ventricular dominance and X-ray screening will show enlargement of the pulmonary arteries and right ventricle, while an ordinary posterior anterior chest radiograph may reveal some enlargement of the cardiac silhouette instead of the small ptotic heart which is so characteristic of emphysema before the development of cor pulmonale. When pulmonary hypertension has existed

for some time arteriosclerotic changes occur in the pulmonary arteries and arterioles, and this adds a further element of structural obstruction to the passage of blood through the pulmonary circulation and increases the burden on the right ventricle. Ultimately the right ventricle fails with the usual evidence of increased venous pressure, liver enlargement, gravitational œdema, etc.

An acute exacerbation of bronchitis or the development of pneumonia—both commonplace incidents in the life of the bronchitic especially during the winter months—may produce rapid deterioration. The bronchioles become increasingly obstructed by secretion, ventilatory insufficiency is further impaired and the degree of anoxia and carbon dioxide retention in the arterial blood is sharply increased. The result is further pulmonary vaso-constriction and right ventricular failure, if it was not present before the acute exacerbation of infection, may develop and progress rapidly.

2. Pulmonary Collapse

The disordered physiology of pulmonary collapse is compared with that of emphysema, a relatively uncharted sea. The most commonplace circumstances in which pulmonary collapse is encountered are after upper abdominal operations, when it is believed to be mainly due to bronchial obstruction by retained inspissated mucus, and in bronchial carcinoma, when the growth itself obstructs the lumen of a bronchus. In such circumstances the lung distal to the blocked bronchus becomes relatively or completely airless and its volume is greatly reduced. In consequence, the diaphragm on the affected side becomes elevated, the mediastinum shifts towards the collapsed lobe and compensatory emphysema develops in the remaining lung tissue. The most important physiological disturbance resulting from pulmonary collapse is that an area of lung becomes unventilated but remains perfused, and, in consequence, blood passing through it is unrepleted with oxygen and has no opportunity of getting rid of its carbon dioxide. It would be thought that this would result in depression of the oxygen content and elevation of the carbon dioxide content of the arterial blood in exact proportion to the amount of lung tissue collapsed, but this is not wholly true. The reasons for this appear to be twofold, firstly, that within a few hours of the development of atelectasis a compensatory partial "shut down" of the pulmonary circulation to the collapsed lung occurs, so that the affected area is perfused much less generously than when it is normally aerated, and, secondly, because the compensatory emphysema in the unaffected lung tissue makes a much larger ventilatory surface available than it offers under normal circumstances, and this, combined with hyperventilation, compensates to some extent for the venous admixture defect occurring in the collapsed segment. The result is that in post-operative atelectasis the degree of arterial oxygen desaturation is much less than would be expected and carbon dioxide retention is unusual, while in more chronic forms of bronchial obstruction, such as bronchial carcinoma, the arterial oxygen content is usually normal. It must be added that in some cases of post-operative atelectasis there are many

widely separated small areas of collapse in the lungs rather than one collapsed lobe, and in these circumstances the compensatory "shut down" of the pulmonary circulation to the affected areas operates far less efficiently and greater degrees of arterial oxygen desaturation are found.

The exclusion from ventilation of a substantial part of the total lung tissue leads to a reduction in all the subdivisions of lung volume and in the maximum breathing capacity. Hyperventilation is commonly present and, in consequence, the breathing reserve is greatly decreased and dyspnœa is usually evident at rest.

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ALVEOLAR-CAPILLARY BLOCK*

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The term "alveolar-capillary block" is an excellent example of expressive nomenclature, indeed it is so vivid that it seems superfluous to define it as an abnormal physiological state due to increased thickness of the tissue planes which separate air in the alveoli from blood in the capillaries of the alveolar walls. The term was first used by Austrian *et al.* in 1951 in a review of "Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion" (Austrian, McClement, Renzetti, Donald, Riley and Cournand, 1951); this is the classic work on this syndrome.

The idea that pathological changes in the alveolar walls caused a specific functional defect was not new and seems to have first emerged clearly in 1922 when Schjerning, in considering the problems of cyanosis, wrote "zu den Gedanken an eine isolierte Schädigung des Alveolar epithals führten nun Brauer klinische Beobachtungen über Zyanose bei den letzten Grippe-epidemien" (Schjerning, 1922). Brauer thus seems to have formulated the pathophysiological concept, although long before, on a purely physiological basis, the importance of diffusion distance in the physics of blood gas exchange was emphasised by the Kroghs and others who established the concept of a purely diffusing, as opposed to secretory, mechanism of gas exchange in mammals (Krogh, 1941; Haldane, 1922; Barcroft, 1925 and 1928).

Ideally, diseases should be classified on the basis of prime causes, but when these are not known the demands of clinical practice impose a wide variety of classes, based to some extent on practical characteristics modified by the prevailing outlook of clinicians. At present we are, broadly speaking, emerging from a predominantly morbid anatomical era into one dominated by functional concepts. This is particularly true of respiratory disorders, in which the development of knowledge of respiratory function is comparatively recent and has been in the hands mainly of clinical physiologists who have relied more on observations on man and on the states resulting from disease than on experiments on animals. Nevertheless, the syndrome of alveolar-capillary block (A-C block) has its anatomical counterpart in the term "pulmonary fibrosis," which in a loose way is used to describe the same syndrome, thus providing an example of a purely anatomical term acquiring a physiological connotation. It has the fault, however, that fibrous tissue is by no means the only element which may be interposed between air and blood in the alveolar wall; fluid, collagen and sheets of cells of both connective tissue and epithelial origin may all play a part.

The production of this A-C block syndrome demands a pathological process which will increase uniformly throughout both lungs the diffusion distance

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between air and blood without at the same time causing extensive narrowing or obliteration of air passages which would cause predominantly the syndrome of alveolar hypoventilation. On the other hand, it might cause extensive obliteration of the pulmonary capillary bed, in which case the physiological and clinical picture would be predominantly one of increase in " dead space," pulmonary hypertension and perhaps right heart failure. Indeed an element of both these processes is commonly present in syndromes of A-C block, but not sufficiently to obscure the predominant diffusion defect. The production of such a selective lesion is naturally a highly discriminating process and it is not surprising that the pure syndrome is rare.

A list of the diseases which have been found to produce it comprises examples of miliary tuberculosis, Boeck's sarcoidosis, scleroderma, radiation fibrosis, lymphangitic carcinomatosis, pulmonary berylliosis, asbestosis, effects of inhalation of sulphur dioxide, chronic disseminated histiocytosis X, and a diffuse granulomatous process following an influenza or a bronchopneumonic type of illness, a process of obscure ætiology which has come to be called the Hamman-Rich syndrome (Austrian *et al.*, 1951; Baldwin *et al.*, 1949; Marks *et al.*, 1957; McClement *et al.*, 1953; Riley *et al.*, 1952; Lyons, 1958; Marshall *et al.*, 1958; Stone *et al.*, 1956; Renzetti *et al.*, 1957; Hamman and Rich, 1944; Rubin and Lubliner, 1957).

It seems likely that detailed physiological studies will establish alveolar-capillary block as an important result of the recently described condition of pulmonary alveolar proteinosis (Rosen *et al.*, 1958).

Increasing refinement in assessing the various aspects of pulmonary function shows that a substantial element of diffusion defect is present in such common conditions as severe mitral stenosis with its inevitable production—among other things—of diffuse pulmonary fibrosis (Carroll *et al.*, 1953). Ætiologically this is a thoroughly mixed group, but all these processes share the capacity of interposing something, whether cellular, extra-cellular or fluid in nature, between air and blood, thus increasing the gaseous diffusion pathway. One of the quantitative factors in gaseous diffusion is that the amount of diffusion per unit time is inversely proportional to the first power of the length of the diffusion pathway. This then is the central point of the concept of alveolar-capillary block.

Physiological Picture of Alveolar-Capillary Block Syndrome

Varied as are the causes of this syndrome, the clinical pictures produced have much in common, dependent as they are on this diffuse alveolar-capillary barrier process. The whole range of mechanisms which are involved can be treated on a physiological basis; indeed, few syndromes lend themselves better to such an approach.

Although not by any means the simplest of measurements the logical first step is to consider the impairment of diffusion which is at the centre of the concept. In this respect it is necessary to remember that oxygen and carbon dioxide differ widely in their diffusibility, owing to the fact that the rate of diffusion of gas is inversely proportional to the square root of its density

(Graham's Law) and the rate of its passage from the gaseous to the liquid phase is directly proportional to its solubility (Henry's Law). The operation of these laws results in the identity of the carbon dioxide tensions of systemic arterial blood and alveolar gas, while in the case of oxygen, which is only about one-twentieth as diffusible, there is, even in health, an appreciable (9 mm. Hg) tension gradient between alveoli and systemic arterial blood. This oxygen gradient, however, is not due solely to blood leaving the pulmonary capillaries imperfectly saturated, that is to a membrane component, but is in health due principally to admixture of blood leaving alveoli, with blood which has either bypassed the alveoli or has passed through imperfectly ventilated alveoli, a small proportion of which are present even in the healthy resting individual.

Reviews of pulmonary diffusion by Forster (1957 and 1959) make it clear that in respect of oxygen the diffusing capacity ($D_{L_{O_2}}$) is the amount of oxygen absorbed in one minute, divided by the difference between the mean alveolar O_2 tension and the mean pulmonary capillary O_2 tension. By the ingenious device of making observations while the patient breathes 14 per cent. O_2, as well as observations while breathing air (Riley and Cournand, 1951), it is possible to estimate the amount of blood which is inadequately oxygenated having perfused relatively underventilated alveoli; this is expressed as the proportion of pulmonary blood flow which entirely avoids alveolar gaseous exchange (per cent. venous admixture). This assumes an " all or none " law, which is not the case, as there are all degrees of alveolar ventilation from perfect to none, but this somewhat artificial expression is in practice entirely adequate. It is also possible to make a similar measurement of alveolar under-perfusion, or over-ventilation, expressing the latter as respiratory dead space, again using the " all or none " convention which converts all grades of under-perfusion to the equivalent volume of zero perfusion.

These expressions of under-ventilation (A-V admixture) and under-perfusion are, when taken together, a measure of inhomogeneity of the ventilation-perfusion ratio. In the nature of things a diffuse pulmonary disease, whether it be any of those mentioned as causing alveolar-capillary block or emphysema, is liable to alter both the diffusing capacity and the ventilation-perfusion ratio, making it essential to measure them individually.

Even when the diffusing capacity is measured the value obtained falls short of the ideal in that it is a value for the whole membrane and not a value per unit area of the membrane. The diffusibility of the membrane is a function, in simple arithmetic ratio, of its area and thickness; a reduction by one-half of the value of the D_L might be due to halving of the membrane area or a doubling of its thickness. Unfortunately there is not as yet any method of measuring the surface area of the alveolar-capillary membrane in living individuals, although the general order of its magnitude is known. Fortunately in practice this inability to distinguish accurately the area and thickness factors of the membrane component is not so serious as one would expect, because collateral information on the divisions of lung volume, radiological appearances, clinical picture, etc., often point strongly to the dimension at fault.

As oxygen requirements are not specifically altered in patients with alveolar-capillary block it follows that the reduction in diffusing capacity is due to increase of the alveolar-capillary gradient, that is the denominator of the $D_{L_{O_2}}$ equation, as the result of increase of the membrane component (Riley *et al.*, 1951; Donald *et al.*, 1952).

The measurement of the $D_{L_{O_2}}$ does not demand much co-operation from the patient, but the technical procedures include the measurement of the CO_2 and O_2 tensions of a sample of arterial blood. This is done by the Riley bubble technique (Riley *et al.*, 1945; Comroe *et al.*, 1955) which is an exacting technical procedure. However, there is an excellent prospect of one or other of the electro-chemical methods of measuring these gases becoming simple and reliable (Clark, 1956; Stow *et al.*, 1957; Severinghaus and Bradley, 1958).

Carbon monoxide can be used in place of oxygen to measure the D_L with the great advantage that it combines so rapidly with the hæmoglobin that the tension of CO in the plasma of the lung capillary is virtually zero. The diffusing capacity for CO can, therefore, be measured if one knows the amount of CO absorbed per minute and the mean alveolar pressure of the gas. If done by the "steady state" method, in which the patient breathes a mixture of air and CO (0·1 to 0·2 per cent.) for about 6 minutes, then the total amount of CO absorbed can be calculated from the concentrations of CO in the closed circuit at the beginning and end of the period. Unfortunately the calculation of the mean alveolar CO concentration necessitates knowing the "physiological dead space" calculated by Bohr's equation, which includes the alveolar CO_2 tension which is regarded as identical with the CO_2 content of arterial blood, making an arterial puncture still necessary. The method, however, has the advantage of being carried out under normal breathing conditions with little co-operation from the patient.

There is a "single-breath" CO method for determining lung diffusion. In this the patient holds for 10 seconds or so a single breath of air containing a low concentration of carbon monoxide (0·3 per cent.) and 10 per cent. of helium. Once again the amount of CO absorbed is obtained from the concentration of carbon monoxide in the inspired breath, less the amount in the expired air, times the volume of alveolar gas. Although this method requires an estimation of the functional residual capacity an arterial puncture is unnecessary as the mean alveolar P_{CO} can be calculated without recourse to data obtained from blood. A comparison of the concentrations of helium in the inspired and expired gas enables calculation of the actual initial alveolar concentration of CO. The simplest (and least discriminating) method of expressing diffusion is to give as a percentage the amount of CO absorbed per minute over the amount inspired; this is called the Fractional CO uptake and is normally about 50 per cent. with values less than 30 per cent. indicating impairment of diffusion. However, a low reading can be due to excessively high alveolar ventilation as well as to impaired diffusion. All the carbon monoxide methods suffer from the disadvantage that there is no means of discriminating between the "membrane component" and the disordered

ventilation/perfusion component in patients with reduced $D_{L_{CO}}$ (Comroe *et al.*, 1955; Krogh, 1914; Bates, 1952; Forster *et al.*, 1955; Bates *et al.*, 1955; Bates *et al.*, 1956).

Although measurements of the alveolar-capillary gradient and the diffusion capacity require somewhat specialised techniques, enough about the A-C gradient can be learned in a rough qualitative way to assist diagnosis. It is important to remember that carbon dioxide is approximately twenty times more diffusible than oxygen and that it is probably well-nigh impossible for the lungs to have their A-C membrane so altered as substantially to impair the outward diffusion of CO_2. In fact, the identity of the alveolar and arterial CO_2 tensions is explicit to the calculation of the $D_{L_{O_2}}$ and the $D_{L_{CO}}$ by the "steady-state" method. Perhaps the only exception is where a patient is in the advanced stages of the alveolar-capillary block syndrome and is maintained alive only by the continuous inhalation of oxygen-enriched air. That being so the observation of a cyanosed patient with a normal or reduced arterial pCO_2 who is free from marked low-output cardiac failure indicates either A-C block or a considerable pulmonary A-V shunt. If the inhalation of oxygen entirely corrects the arterial unsaturation, then A-C block is incontestably the dominant defect. However, in the very nature of things, the same pathological process that causes the block often causes quite marked A-V shunting. This is merely another way of saying that the thickening of the membrane has proceeded so far in so many alveoli as to stop diffusion of oxygen, even at artificially high gradients, with the result that even inhaling oxygen does not entirely abolish the arterial unsaturation but raises it for example from 92 to 98 per cent. saturation, then one is entitled to presume a diagnosis of A-C block. It is only in the advanced stages of the A-C block syndrome that there is marked arterial unsaturation at rest, that is values below 90 per cent. In suspected cases it is important to take a sample of arterial blood immediately after exercise; this need not be strenuous, for example, a level of only treble the resting O_2 consumption is sufficient. A marked drop in saturation, provided always the CO_2 is not elevated and there is no gross cardiac defect, is then diagnostic of the A-C syndrome.

Any pathological process, whether cellular infiltration, the formation of connective tissue, or the deposition of some abnormal substance which diffusely thickens alveolar walls in the lungs, is likely at the same time to increase the density of the lungs and to make it harder to distend them. The author had a practical illustration of this ten years ago during the investigation of a patient who subsequently died with a pathological process resembling the Hamman-Rich syndrome. A bronchoscopy was performed under anæsthesia induced by an intravenous barbiturate, followed by a muscle relaxant. The anæsthetist then attempted, in the usual way, to ventilate the patient by compressing the bag attached to the cuffed intratracheal catheter; he was astonished to find that instead of the lungs distending easily his compression of the bag was abruptly arrested by unaccustomed resistance. The rubber-like consistency of the lungs displayed at autopsy some weeks later adequately explained this phenomenon. The sudden arrest of inspiration when a deep breath is attempted

is often easily recognised in this syndrome and has come to be called the " door-stop " sign. The effect of this on the statics of lung volumes is to cause a great reduction in the inspiratory capacity with a proportionate reduction in the vital and total lung capacities. As there is no airtrapping the residual volume is normal, but the reduction of total capacity leads, of course, to a high RV/TLC ratio which is usually around 50 per cent. rather than its normal value of 20-30 per cent. It is almost certainly this resistance to distension which leads to the excessive acceleration of respiration on exercise and in established cases the tachypnœa at rest which characterises the A-C syndrome. This results in a high resting ventilatory volume (or ventilation equivalent) which by alveolar over-ventilation accounts for the fact that the pCO_2 may be abnormally low (<40 mm. Hg).

As the pathological process does not cause constriction of airways gas mixing is normal. This means that after 7 minutes' breathing pure oxygen the expired gas contains less than 2·5 per cent. of nitrogen, that the mixing efficiency of helium in a closed circuit is at least 76 per cent. of the ideal, and that gas distribution tested by measuring the nitrogen in the expirate immediately following a breath of pure oxygen using a continuously recording nitrogen-meter shows no more than 1·5 per cent. increase of nitrogen from 750 to 1,250 ml. of expired gas (Comroe *et al.*, 1955).

The absence of impairment of bronchial airflow accounts for the normal results of airflow tests such as the maximum breathing capacity or the maximal expiratory flow rate. The normality of these airflow and mixing tests is in sharp contrast to the findings in pulmonary emphysema, which clinically may resemble the A-C block syndrome, in that it is associated with dyspnœa, tachypnœa and cyanosis, accentuated by exercise and abolished by inhaling oxygen. The character of the spirogram is essentially normal, showing none of the retardation of the down slope and progressive elevation of the resting respiratory level on forced breathing which characterises the bronchial obstruction and air trapping of emphysema.

This diffuse deposition of new material throughout the lungs makes them stiff and resistant to distension, a fact which can be shown during life by the " work " or pressure volume diagram of the lungs during a single respiration (Comroe *et al.*, 1955). This constitutes a plot of the simultaneous values of intrathoracic pressure recorded by a manometer whose bulb is in the œsophagus and the volume displacement recorded by an integrating pneumotachograph or a special spirometer (Lillie, 1950; Arnott *et al.*, 1954). The long axis of the " loop " is tilted from the normal because of the diminished volume change per unit change of pressure, or diminished compliance as it is known technically. At the same time the area of the loop is not increased, showing that there is no increase in the non-elastic work of propelling air through the bronchi. This demonstration that the increased work of breathing is due to diminished pulmonary elasticity affords a clue to the characteristic rapidity of respiration which contributes more than increased tidal volume to the high minute ventilation.

Christie (1953) pointed out that the rate and depth of breathing is adjusted

to levels which are most economical in terms of respiratory work. The proportion of work done in overcoming elasticity increases as breathing becomes slower and deeper, whereas the proportion of work performed in overcoming the viscous-turbulent hindrance to airflow increases with the rate of breathing. This adjustment seems to be made through the Hering-Breuer reflex, whose sensory end-organs in the lung parenchyma are subjected to abnormally powerful inspiratory stimuli, as the result of the stiffening process. Cournand supports this hypothesis, pointing out that the hyperventilation is maintained despite a normal arterial pO_2 (as it often is at rest in these patients) and a normal or reduced pCO_2. Another factor which may stimulate hyperventilation is that the normal pH of the blood with reduced pCO_2 constitutes a state of respiratory alkalosis in which the alkali reserve is abnormally low. This state heightens the sensitivity of the respiratory centre to carbon dioxide. This contrasts with conditions in the alveolar hypoventilation syndrome, *e.g.* emphysema, in which CO_2 is retained, thus reducing the sensitivity of the respiratory centre to CO_2. Of course, in the A-C block syndrome arterial O_2 tension is reduced even at rest, when the condition is advanced, and in all but the earliest cases during exercise; this increases the respiratory drive through the carotid sinuses.

It is not to be expected that such a diffuse and profound pathological process would be without effects on the circulation through the lungs. Hypertension, both systolic and diastolic, in the pulmonary artery, with a normal pulmonary capillary pressure is the usual state of affairs. Although in the earlier stages the pressures may be normal at rest, mild exercise at once induces hypertension, thus displaying the indistensibility of the pulmonary vascular bed. Harvey *et al.* (1951) regard the anatomical changes as playing the main part in the hypertension, although during exercise anoxia may contribute. Pulmonary blood flow is usually normal, unlike its status in emphysema in which it is sometimes elevated, and if cardiac failure supervenes the output falls progressively. The relative severity of vascular hypertension as compared with the diffusion defect varies widely, ranging from death due to pure respiratory failure with anoxia the chief agent and the right heart unimpaired, to severe pulmonary hypertension with right heart defect and virtually normal pulmonary diffusion. In fact it may be, although this is speculative, that some forms of so-called primary pulmonary hypertension are vascular extremes of a basic pathological process which may otherwise show itself as alveolar-capillary block.

Pathological Features

Based as the pathology is on a wide range of ætiological agents, there are naturally considerable differences in the morbid anatomy, but there are at the same time certain fundamental similarities. In all there is an abnormal solidity of the lungs. They are unduly firm to the grasp, not so much the firmness of the œdematous or pneumonic lung, but a characteristic somewhat elastic, often described as rubbery, consistency. In appearance there is commonly diffuse pleural thickening with obliteration of the interlobar septa by a

dense network of filmy adhesions and attachment of visceral to parietal pleura. Histologically there is diffuse thickening of the alveolar capillary septa which constitutes the essential lesion. The nature of this thickening varies in detail according to the nature of the individual causes. Sometimes there are patches of emphysematous change, as it cannot be expected that these processes will be uniform in their effect. This latter change accounts for certain minor departures from the pure physiological picture as described.

Clinical Features

In most varieties the onset is insidious, although in the Hamman-Rich syndrome an initial febrile illness of respiratory type clinically indistinguishable from influenza is usual. The initial, and in progressively more severe degree throughout, disturbance is dyspnœa. This is not a laboured obstructed breathing pattern like chronic bronchitis or asthma, but essentially a gross increase of ventilatory volume, secured mainly by increase in rate rather than depth. In the early stages the tachypnœa is absent at rest but at once becomes apparent on exercise, while in the established disorder the resting respiratory rate is at least 20 per minute and may be continuously as high as 35-40 per minute in the later stages. In fact the author has been able to arrive at the diagnosis while approaching the patient by observing the chart showing respiration around 30, with little or no fever, lasting for weeks. The rate falls little during sleep. Orthopnœa is absent, except when pulmonary hypertension has led to right heart failure. Tachycardia is quite often present. Cyanosis is usually absent at rest until the later stages, when oxygen values of arterial blood may fall to values as low as 60 per cent. However, cyanosis can usually be appreciated when even mild exercise is taken. Clubbing of the digits is capricious in its occurrence, depending as it does on mechanisms whose explanation remains a challenge to the clinical physiologist. Cough is usually present and sputum is usually scanty and non-purulent. Extreme fatiguability is an early feature and, as arterial unsaturation becomes established, weight is lost.

Owing to the absence of carbon dioxide retention the mental state is usually comparatively clear until the terminal stages, although headache and anorexia are common. In fact, the general upset is dependent on pure anoxia rather than anoxia plus carbon dioxide poisoning, as in emphysema. In this respect the picture approximates to that of mountain sickness. Polycythæmia is rarely present, probably because the anoxic stimulus to the marrow is not prolonged or intense enough to induce this reaction. Indeed, when the condition is due to a disseminated collagen disorder anæmia may occur.

Clinical examination of the chest usually reveals some moist accompaniments to the normal vesicular breathing, but there is a striking absence of dry continuous accompaniments and other signs of bronchial narrowing. When pulmonary hypertension is present a hand placed over the upper part of the sternum detects the heave of the right ventricular outflow tract followed by the thud of the slamming pulmonary valve. Later all the signs of congestive cardiac failure may supervene. In addition there may be signs peculiar to the causal disease.

Most patients with the alveolar-capillary block syndrome deteriorate and die within a matter of a few months, death occurring often from some superadded respiratory infection which would be trivial in a normal person but is insupportable on top of the block disability. Sometimes this final fatal infection is due to an antibiotic resistant pathogen—for example, the *Candida albicans*, whose pathogenicity may be assisted by the fact that the patient is being treated by corticoids.

Radiological Features

Diffuse distribution throughout both lungs is once again the principal characteristic. In detail the picture varies with the cause, but generally it consists of a fine reticular or granular appearance. It is important to realise that the features may not be striking until a late stage, and it is possible for quite a severe degree of block to be present, with radiological changes that might escape detection on a cursory glance. Pleural thickening and adhesion may be shown by the obliteration of costophrenic angles and the prominence of fissure lines.

Diagnosis

Clearly the diagnosis of alveolar-capillary block can be precise when the resources of a modern cardio-respiratory laboratory are available. Because of the range of equipment and technical skill necessary these are not yet freely available. There is here a fruitful field for instrument technology which, as knowledge of respiratory function extends, will simplify and extend the availability of these investigations.

A reasonably accurate diagnosis can be made on the basis of dyspnœa, hyperventilation and tachypnœa, the presence of diffuse finely dispersed radiological pulmonary lesions and an absence of evidence of bronchial obstruction or emphysema. The addition of cyanosis on exercise which can be completely abolished by breathing oxygen-enriched air greatly strengthens the clinical diagnosis. When pulmonary hypertension with right ventricular hypertrophy is present, it may be impossible to exclude without catherisation a congenital cardiac defect such as a ventricular septal defect or a patent ductus arteriosus with reversed, that is right-to-left, flow.

The diagnosis of A-C block is greatly strengthened by the recognition of the causal disease by a gland biopsy showing sarcoidosis, or by a history of exposure to beryllium or therapeutic radiation to the chest, etc. In view of the possibility of effective corticoid therapy a lung biopsy may be a justifiable procedure when all other diagnostic measures have failed, but this is not a trifling procedure and may for a time at least add to the respiratory disability. The mistake has undoubtedly been made of regarding cases of A-C block as suffering from a pure neurosis, mainly on the bases of the sustained rapid respiratory rate; modern knowledge should exclude this error.

To avoid confusion it should be emphasised that the clinical diagnosis of alveolar-capillary block syndrome is limited to conditions in which this defect is overwhelmingly predominant.

Treatment

There are some general therapeutic principles as distinct from those directly related to the ætiological process. Limitation and, if possible, the reduction of the blocking substance by a corticoid should be attempted and may in some disorders like sarcoid, radiation fibrosis, the collagen diseases, etc., lead to remission. Oxygen inhalation will correct the anoxia, but in the face of a disease advancing inexorably the patient will become increasingly dependent on his oxygen lifeline. There is no physiological contraindication to oxygen therapy provided the concentration is not too high; 50 per cent. is perfectly safe, as CO_2 retention, in contrast to ventilatory insufficiency, is absent. Apart from prompt antibiotic treatment of intercurrent infection no other treatment is useful (McClement *et al.*, 1953; Riley *et al.*, 1952; Stone *et al.*, 1956; Renzetti *et al.*, 1957; Rubin and Lubliner, 1957; West *et al.*, 1951).

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THE MANAGEMENT OF RESPIRATORY INFECTION

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Infections of the respiratory tract commonly start in the upper respiratory passages and are usually due to the viruses of the common cold, influenza or the adenoviruses. These are highly infectious and as yet not noticeably amenable to preventive vaccination or chemotherapy. They are prone to excite secondary bacterial infection both locally and in the lower respiratory passages. Laryngitis and tracheitis are especially serious in infants and children because of the obstructive effects in their smaller air passages. Virus infection of the lung itself is rare in civilian practice in this country and a diagnosis of virus pneumonia is rarely warranted. Atypical primary pneumonia was seen in wartime but is not often found now; psittacosis and Q fever are rather exceptional. Epidemics and the presence of a cold agglutinin and a rather peculiar X-ray appearance may suggest their occurrence, but as a rule bacterial infection is the manifestation in the bronchi and lungs associated with acute respiratory infection.

Bronchitis has special features because of its explosive development and diffuse and bilateral extent. The toxæmia may be slight and symptoms are more the result of bronchospasm and mucus production causing obstruction. Difficult expiration is most marked, though interference with airflow and loss of lung compliance add to the mechanical difficulties of breathing. The nature of bronchospasm is not clear and may well be largely anaphylactic, as the asthmatic character of the symptoms in many cases exceeds the inflammatory and the toxic. A rising pulmonary artery pressure is also associated with the infection and has its own deleterious effects on the pulmonary circulation and the right heart. Individual susceptibility and heredity are both important features in the development of this condition. The development of emphysema occurs sooner or later. It may be very rapid after only one slight attack or it may be delayed and result from numerous attacks over many years. It leads to permanent ventilatory defects. Antibiotics help to limit the bacterial infection and should be used early to shorten the period of high pulmonary artery pressure, but symptoms are often prolonged beyond elimination of the bacteria from the sputum. For the troublesome bronchospasm steroids often play a useful part, and ACTH by injection is effective, but of course requires frequent injections. The alternative is Brockbank's method of oral cortisone beginning with a large dose and reducing rapidly. The use of trypsin inhalers and other methods of attempting to reduce the viscid character of the sputum are not very effective, though steam is still of advantage. For prophylactic use long courses of Tetracycline have been recommended and may help some patients. The use of vaccines to combat the allergic reaction associated with the bronchitis seems rational, but it is difficult to reproduce the bacterial flora. That of the postnasal space often reflects a probable picture, but variations sometimes make the

effect disappointing. Oxygen and antispasmodics, particularly aminophylline, are of great symptomatic value. The former, of course, need care because of carbon dioxide retention in chronic cases. At the moment the tendency is perhaps not to use oxygen sufficiently; anoxia and hypoxæmia are important and dangerous states which must be corrected.

Pneumonia has largely changed in its character from the old classical lobar pneumonia to either a descending bronchiolitis with bronchopneumonia or some form of aspiration pneumonia with a factor of atelectasis. Resulting from influenza the lung infection is usually bacterial and the influenza virus is only rarely found and in small numbers, except in those fulminating and deadly cases that sometimes appear during severe epidemics. Most cases of pneumonia readily respond to the antibiotics, but the resistant staphylococcus is an awkward complication occasionally met. The most difficult situation to treat is the scattered bronchopneumonia in lungs already severely damaged by bronchitis and emphysema. Here again the factors of respiratory obstruction, carbon dioxide retention, viscid sputum and right heart failure produce a vicious circle. It is in these cases that tracheotomy has its great advantages. By reducing the dead space, increasing the oxygen inhalation to a high concentration, and aspirating bronchial secretions from those patients unable to cough them up, many cases are relieved who would otherwise quickly die. Indications are that it should be done early if at all and in patients with inability to cough and where there is sticky sputum and a rising pCO_2. If necessary, artificial ventilation can be carried out through the tracheotomy. When tremor, convulsions, coma, and the other signs of CO_2 poisoning have developed, the situation is acute. When using potent antibiotics for pulmonary infections it must be remembered that superadded fungal infections sometimes occur, particularly in the pneumonic areas; for instance, aspergillus with a mycetoma and other monilia may be found. It is also necessary to remember the possible presence of actinomycosis.

Bronchiectasis is perhaps less commonly seen in its florid state in these days because of the better treatment of the fundamental causes of atelectasis and superadded infection. These need not occur at the same time, and adequate treatment of primary tuberculosis with atelectasis or whooping cough and prevention of its pneumonic complications reduces the possibility of continuing atelectasis. Two types of bronchiectasis are seen clinically: first, the localised lobar atelectactic lesion, usually as a result of some early bronchial obstruction, and this, of course, is particularly amenable to surgery. The other type, especially from whooping cough or other aspiration pneumonic infection, is more scattered, often bilateral and associated with bronchitic changes which make surgery much less effective or even possible. Persistent postural drainage is the clue to effective treatment, but is difficult. Frequent physiotherapy and frequent use of antibiotics give much relief. The difficulty is to arrange sufficiently often the use of antibiotics.

Tuberculosis is hardly in the scope of this paper, but it is worth perhaps emphasising the different modes of presentation in these days. Mass radiography often shows the difficulty of assessing activity and the need for treat-

ment, which should not be embarked on lightly when it can be troublesome, potentially dangerous and very prolonged, unless there are particular reasons for demanding it. Another point to remember is that the disease is being found more often in patients over the age of 40, especially in the male sex. The odd onset in patients with vague respiratory infection without the usual characteristics of tuberculosis demands the use of X-ray examination for any persisting respiratory symptoms.

Another very important diagnostic problem is the early stage of bronchial carcinoma. The so-called unresolved pneumonia is very frequently the beginning of a bronchial carcinoma, and the label " unresolved pneumonia " should never be used diagnostically, but should be an indication for investigation. X-ray changes may give a complete answer, but with the vague appearances procrastination is not the way to discover the disease if effective treatment is to be considered. Early bronchoscopy and, if necessary, thoracotomy are additional measures that should be applied. Early and effective surgery can offer patients a more than 21 per cent. chance of surviving ten years.

Empyema from pneumonia is perhaps less common in these days of antibiotics and has often a quiet onset which may make diagnosis difficult. Sometimes the cases are ambulant and come to out-patients. Aspiration of post-pneumonic effusions should always be carried out and, if the fluid is only just turbid, early and persistent aspiration may relieve the condition, though pleural thickening can be troublesome. Drainage in the intermediate stage can still be used, but, if the condition is at all prolonged, thoracotomy and decortication of the lung lead to quick cure and early restoration of respiratory function.

In conclusion, a word must be said about prophylaxis of respiratory infections. Work is going on to obtain effective vaccination against virus infections, but as yet the variability of the virus makes its use, except in epidemics, unreliable. Bronchitis also gives great problems for prophylaxis. Long-term winter Tetracycline administration has been tried with moderate success. Vaccines sometimes help against the development of bacterial sensitivity and asthmatic features of the condition. Air pollution is being tackled, but the climate in this country is especially disadvantageous and can be avoided only by a few.

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THE MANAGEMENT OF STATUS ASTHMATICUS

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From the United Birmingham Hospitals

Although asthma is typically a disease of paroxysmal recurrences, the acute attack may persist, sometimes for days or weeks, as status asthmaticus. In reviewing the management of status asthmaticus some way of defining this term is necessary, and it has here been taken to be appropriate in those patients whose attacks had been of sufficient severity or duration to have necessitated their admission to hospital. The last 100 cases of status asthmaticus admitted to the General Hospital, Birmingham, under the care of the author, have been collected here, and the methods of treatment will be discussed. Most of these cases have been sent in by their practitioner because they have failed to respond to treatment at home by the usual measures, adrenalin, ephedrine, inhalers and sometimes parenteral aminophyllin. Only those who have not responded to treatment in the Casualty Department and have then needed admission are included here. The duration of the attack before admission has been very variable, but has not usually been less than 12 hours, and some patients have been disabled and bedridden for many weeks in a state of continuous bronchospasm. It has not been felt worth while differentiating between the patient admitted for an acute severe attack and the patient admitted for chronic intractable asthma.

Material

In this series of 100 admissions there are rather more men than women, in a ratio of about 3 to 2, but in both males and females there have been many more admissions over the age of 40 than under, about three-quarters of the whole series being between 40 and 67. Children are not admitted to this hospital and do not, therefore, appear in this series, but apart from this selection status asthmaticus does seem to occur more commonly in the older age groups.

Although there can be many factors precipitating an attack of asthma, these may be roughly divided into three groups—allergic, infective and psychological. By " allergic " is implied a response to some external allergen, inhalant, food, drug and so on, and this allergic group does not include those in whom endogenous bacterial allergy might be incriminated, these being called infective. Estimates of the relative importance of these factors are not agreed in the literature, and seem to vary with the particular interest of each writer. Probably the factors vary at different periods of life, allergy being more pronounced in the child than the elderly. In this series the infective group was considerably larger than the allergic, the psychological group being the smallest. This division may be reflected in the higher incidence of admissions in older people in whom chronic respiratory infection is more common. That infective asthma is rather more intractable may also be shown by the fact that the average

length of stay in hospital was fifteen days in the infective group, compared with ten days in the allergic group.

There is some seasonal variation in the rate of admissions for status asthmaticus, with peaks in mid-winter and late summer. Exclusion of the allergic cases considerably diminishes this summer peak, but does not remove it, and perhaps some of the cases considered as predominantly infective may have allergic factors that have been somewhat obscured.

General Management

There is no doubt that in many cases of status asthmaticus the simple removal of the patient to hospital will of itself allow the attack to subside. Where this happens it suggests that there are some potent allergic factors in the patient's own environment, and that as long as these allergens are present in high concentration antispasmodics are not effective. The other possible explanation is that there are intolerable psychological factors at work from which escape into hospital is the only immediate solution. The ideal might be to have an atmosphere from which all inhaled allergens are excluded, and some centres in America have asthma rooms where the air is filtered and where bedding and furnishing is of a type such as to reduce dust formation to a minimum. The General Hospital, in the centre of the City of Birmingham, was built at the end of the nineteenth century and has the plenum system of ventilation, the internal air being filtered and warmed. Closed windows, and a surrounding brick wilderness, effectively exclude any high concentration of pollens, and in this at least the building may have advantages over those of more modern construction.

Environment having been controlled as adequately as possible, the most pressing need is to relieve anoxia. This can only be partially achieved by administering oxygen, and relief of respiratory obstruction is the greatest necessity. This obstruction is due to œdema of the bronchial mucosa, to constriction of the bronchial muscles and to excessive mucus secretion, particularly when this coagulates and forms casts of the bronchioles. Bronchodilators, such as adrenalin, probably act as much by lessening the œdema as by relieving the bronchospasm.

Drugs

To the drugs traditionally used in asthma there have been only two major additions in the last twenty years. These are aminophyllin and the corticosteroids. Adrenalin and ephedrine and their related compounds are the most widely used drugs for attacks of asthma, and in most cases are quite effective, especially if given early. There is a good deal of synonymity between adrenalin-resistant asthma and status asthmaticus, and it is where adrenalin has failed that admission is most often sought. Occasionally slow subcutaneous injection of a larger dose of adrenalin up to 2 ml. over the course of 15 to 20 minutes is effective when the usual smaller dose has failed, but where adrenalin resistance has occurred adrenalin is best avoided. In this series adrenalin

terminated the attack in 4, the remainder being adrenalin resistant. As these 4 had already had adrenalin without effect before admission it may have been the combination with antibiotics or sedatives, or the change of environment, which restored its effect.

Ephedrine and its related substances act perhaps by slowing the rate of destruction of adrenalin, and they are not usually successful in status asthmaticus when adrenalin resistance has occurred. In older men too, in whom there may be some degree of prostatic obstruction, acute retention of urine is sometimes precipitated by ephedrine.

Isoprenaline is probably the most effective of the inhaled antispasmodics, usually in a 1 per cent. solution. The effectiveness of inhaled solutions depends on the size of the droplets, only the smallest, below 10 μ in radius, reaching the bronchioles (Abramson, 1949). Larger droplets are deposited on the mucosa of the upper respiratory passages, whence they must be absorbed and circulated before they can be effective. There is now a pocket unit in which Freons are used as a vehicle for isoprenaline, and in this a valve mechanism allows ejection of a measured dose in a fine cloud of aerosol particles, and this is proving a most useful appliance.

When adrenalin and its related compounds have failed aminophyllin is the great standby, and its introduction into the treatment of asthma about twenty years ago was a major advance. Orally given, its effect is slow and uncertain and it is used mainly prophylactically. Its use is limited by gastric irritation, but this can be lessened by the simultaneous administration of an antacid such as aludrox, or by using the newer derivatives such as choledyl or etophyllate, which can be given in considerably larger doses.

In status asthmaticus aminophyllin is preferably given intravenously in a dose of 0·25 to 0·5 g. It must be given slowly, diluted to 10 to 20 ml. Syncope and peripheral vascular collapse can occur if the injection is too rapid, and a rate of 1 ml. a minute is suggested. In a protracted attack, when response to a single dose of aminophyllin is not long maintained, continuous infusion can be employed, and a solution of 0·5 g. in a litre of 5 per cent. dextrose is given by intravenous drip, up to 3 litres a day. When several injections of aminophyllin are necessary each day this technique is probably preferable, and it can, of course, be combined with ACTH should this be desired.

Intramuscular aminophyllin, in similar doses, is somewhat painful and probably less effective, but can be used when the intravenous route is for some reason impracticable. Aminophyllin can also be given rectally, usually as a suppository of 0·5 g., and many patients find this quite effective in dealing with attacks of asthma and in preventing nocturnal attacks.

In this series intravenous aminophyllin was given to practically all the patients, and, although the dose often had to be repeated, it finally brought the attack under control in 43 of these cases.

The Use of Steroids

The great advance in recent years in the treatment of status asthmaticus has been the introduction of steroids. The early reports date from 1950, and

although the place of cortisone in chronic asthma and its use in long-term treatment is still debatable, there is general agreement as to its effectiveness in status asthmaticus. The M.R.C. trial in 1956 used cortisone rather than ACTH because it was becoming freely available at that time and could be given by mouth (Medical Research Council, 1956). In this trial patients who were still in status asthmaticus after 24 hours of standard antispasmodic treatment in hospital were given a nine-day course of cortisone acetate beginning with 350 mg. on the first day, then 200 mg., reducing by 25 mg. each day. The majority of these patients were getting relief by the fourth day, but in a similar control group only a small proportion gained comparable relief. Other series have shown similar results and it has now become the general practice to use steroids when other treatment is proving ineffective.

In this series of patients, when the bronchospasm has persisted in spite of antispasmodics, and is apparently continuing, ACTH has usually been used. Most of these patients have had more than 24 hours of hospital treatment before starting ACTH, but there have been a few in whom it was apparent from the experience of their treatment in previous admissions that ACTH would be necessary, and in these it has been started, in combination with antispasmodics, at an earlier stage. ACTH has been used rather than cortisone because it has been an impression that intravenous ACTH more rapidly brings the status under control. There are certainly a few patients, 2 in this series, in whom this régime was effective when cortisone had failed. On the other hand, 4 patients were not controlled by ACTH and were then relieved by cortisone. The practice has been, when ACTH is used, to give 25 units in 500 ml. of 5 per cent. dextrose by intravenous drip over the course of 6 to 8 hours, and to give this dose on three successive days. Many patients experience relief during the course of the first infusion and, although a few patients have been given seven to ten daily infusions, in most improvement has occurred by the third day and is less likely if it has not occurred by then. It would perhaps be an indication to change over to cortisone if three days of ACTH had not shown some beneficial effect. ACTH gel, given intramuscularly, seems much less effective, and although it has been used in maintenance it probably has little place in the management of status asthmaticus. There has recently been a change in the measurement of the unit of ACTH when given intravenously, and the 25 units referred to above appear to correspond to 75 units of the present preparation.

In this series it was felt necessary to use steroids in 51 of the 100 cases, and in 44 of these 51 ACTH was used. In all but 8 of these it provided complete relief, including 2 where cortisone had failed. Cortisone was used in 15 of the series, successfully in 10, in 4 of whom ACTH had failed. The dose of cortisone has to be surprisingly large, and less than 200 mg. is unlikely to be effective. A scheme of dosage has been used like that given in the M.R.C. trial, or that suggested by Brockbank (1957) where 300 mg. of cortisone acetate is given on the first day, that is twelve tablets of 25 mg., followed by a dose decreasing by one tablet each day so that the total course last for twelve days. With this short course the side effects of cortisone treatment, moon-face, water retention and so on, do not usually occur, and, by adopting a set course, the risk of being

left with a cortisone-dependent patient is minimised. This limited course can be repeated at reasonable intervals if necessary, and seems preferable to the scheme suggested by some American workers (Irwin and Burrage, 1958) where a so-called clearing dose of cortisone is given, 300 mg., followed by 200 mg. daily until the signs of asthma are cleared, then a reduction to a maintenance dose high enough to prevent bronchospasm recurring. This maintenance dose usually needs to be rather high, of the order of 75 mg. or more a day, or its equivalent in prednisone. For the limited course of treatment prednisone does not seem to have any substantial advantage over ordinary cortisone acetate.

There are other ways of administering steroids which might be mentioned. In the acute shock-like state which sometimes occurs in severe status asthmaticus, hydrocortisone hemisuccinate intravenously may be helpful. In one recent patient, not in this series, there was undoubted benefit, but ACTH had to be given subsequently before the bronchospasm was controlled. Hydrocortisone has also been given topically, either as an aerosol solution or as an insufflated powder. In a controlled trial (Franklin *et al.*, 1958), there appeared to be statistical evidence that aerosol hydrocortisone was effective in doses much smaller than would have been effective systemically, and the effect seemed to be due to a local action rather than to systemic absorption. The published reports deal mainly with the prophylactic use of hydrocortisone inhalations, and do not indicate much immediate effect, and it is the general experience that there is little relieving effect during attacks of asthma (Brockbank *et al.*, 1956). Another effect of steroids that has been noticed by some workers is the restoration of the effect of adrenalin in a previously adrenalin-resistant state (Duner, 1957).

Complications

Dangers, however, are always present and especially so in patients who already have a respiratory infection. There were five examples of acute respiratory infection arising during the course of treatment with steroids, one with a penicillin-resistant staphylococcus. These responded to antibiotics except in one case.

This was a man of 47 who was admitted for a third time in status asthmaticus, having had rather severe asthma since an accident in which he suffered burns two years previously. In a previous admission ACTH had only given slight relief. His X-ray showed nothing more than some emphysema and his sputum contained no particular pathogens. Response to the usual measures, antibiotics, choledyl and intravenous aminophyllin, was poor, and after ten days he was started on cortisone. On the sixth day after he had had 900 mg. he had a sudden pain in the right lower chest and pyrexia. During the following night he became very short of breath and coughed up blood, and he collapsed and died 24 hours after the onset of the pain. An X-ray taken during this period showed a very large cavity in the right lower lobe, and this was confirmed at autopsy, which showed acute lung gangrene, the cavity containing air, blood and necrotic lung tissue.

There have been two other deaths in this series.

A woman of 45 had had winter bronchitis for some years and was admitted with acute asthma after three days of malaise and pyrexia. She was treated with antibiotics and intravenous aminophyllin and improved a little, but worsened the following day. This time there was no response to intravenous aminophyllin, oxygen, and intramuscular cortisone, and she died in acute bronchospasm while an ACTH drip was being set up. Autopsy showed acute tracheitis and bronchitis and emphysema.

The other death was a man of 48 who had been admitted to hospital in status asthmaticus on a number of occasions, the condition being regarded as mainly infective, but with a considerable psychological element. Previously he had responded quite well both to ACTH and to cortisone, but he had been on a maintenance dose of 50 mg. of cortisone for some months. He was admitted after a week of status asthmaticus and again responded well to intravenous aminophyllin and three doses of ACTH intravenously. He was well and walking around the ward and ready for discharge when a further severe attack of asthma came on, and he died within 15 minutes of the onset. At autopsy the lungs were acutely emphysematous.

Another patient with a similar history does not appear in this series.

He was a student whose attacks seemed to be brought on only mainly by psychological factors, but these were of a severity that had needed admission to hospital, and ACTH on several occasions. Following psychiatric help he seemed very much improved, but another acute attack of asthma developed at home and he died within half an hour.

It used to be said that an asthmatic attack is never fatal, but quite a number of asthmatics, after having survived many hundreds of attacks, do actually die of asthma. A series of cases of fatal asthma was described and the literature reviewed by Earle, and by Houston *et al.* (1953). I do not feel that the last two deaths here described are directly due to the use of steroids, and these patients might well have died earlier had steroids not been used. The mode of death, however, does seem to follow a rather striking pattern, with a very sudden onset of asthma during a phase when the patient was apparently free of bronchospasm, and a rapid death in a state of asphyxia and shock, and this pattern seems somewhat different from the majority of fatal asthmatic attacks in Earle's series. Brockbank (1957), however, described seven similar deaths in a series of patients who had needed long-term oral cortisone to control their asthma, and some of these patients were later found to have some degree of adrenal atrophy. Whenever steroids are used, antibiotic cover is advisable, and penicillin and streptomycin or tetracycline are given at first, altering this régime if necessary when bacteriological examination of the sputum has been done. Recently nystatin has been given in addition, as monilia seems to appear quite frequently in the sputum as well as causing oropharyngeal infection.

Sedation

Sedation in asthma is not an easy problem. There is no doubt that, as in hæmoptysis, morphia can be very dangerous, and it should never be used.

Barbiturates given in reasonably small doses do not seem to produce enough respiratory depression to cause trouble in the ordinary asthmatic, but their use is unwise in patients with chronic respiratory failure and carbon dioxide retention. Chloral hydrate and paraldehyde are probably safer than barbiturates, and the sedative effect of antihistamines may be useful, although they have little or no direct effect on asthma. None of these drugs, however, is entirely free from respiratory depression. Several patients have reported some help from chlorpromazine, and although it does not have much prophylactic effect in psychogenic asthma it can be a very useful sedative in the acute attack. Measurements made of respiratory function after 25 and 50 mg. of chlorpromazine intramuscularly (Baum *et al.*, 1957) led to the conclusion that it would induce relaxation quickly, with no respiratory depression, and that it was probably the safest sedative to use in asthma.

Other Measures

Coughing itself aggravates bronchitis and bronchospasm, and unnecessary coughing sometimes becomes a habit, and can even induce an attack of wheezing. Some degree of suppression of cough can be achieved by the patient's own efforts, but all respiratory irritants should be excluded and if cough is very troublesome steam inhalations are useful. Many patients who have died in status asthmaticus are found to have their terminal bronchi plugged by tenacious mucus casts, and a satisfactory method of liquefaction of these casts would be of the greatest value. Dehydration may be a cause of this inspissation of mucus, and rehydration of the patient and humidification of the atmosphere is then necessary. Intravenous 5 per cent. glucose has been advocated, and perhaps the intravenous infusion necessary for giving ACTH plays a part in its effectiveness. Unless the patient is adequately hydrated the effect of expectorants is likely to be negligible. Recently the inhalation of detergent solutions, such as Alevaire, and of proteolytic enzymes has been tried. They seem to be of most value when the patient is conscious of sticky sputum in his trachea but is unable to dislodge it in spite of exhausting paroxysms of cough. These are the circumstances in which bronchoscopy might be advocated, and some bronchoscopists have reported on several hundreds of asthmatics in whom bronchoscopy has been considered necessary (Waldbott, 1949). The main indication is to prevent a moribund patient being asphyxiated by an accumulation of mucus. A patient whose condition is deteriorating and whose expectoration is gradually becoming more scanty and difficult, or one whose sputum contains bronchial casts and in whom each coughing spell results in more wheezing, evidence that sputum is not being coughed up, may be helped by bronchoscopy, and removal of 90-120 ml. of mucus is reported. Other indications in status asthmaticus are to remove single plugs causing lobar or pulmonary atelectasis, to remove secretion from bronchiectatic areas, and to dilate strictures following inflammatory change. In asthmatics bronchoscopy is best done with as little anæsthesia as possible, with intravenous aminophyllin before and continuous oxygen during the procedure, and saline lavage may help if mucus is difficult to aspirate.

In this series very few bronchoscopies have been done and these mainly because there had been some reason to suspect an underlying carcinoma. No large quantities of mucus have been seen, nor the strictures reported so frequently as in some series. A good physiotherapist can often do as much as, or more than, a bronchoscopist, and the main indication will be where there is obvious retention of, and obstruction by, secretion which cannot otherwise be dislodged.

Oxygen and helium has been used in asthma, and its use would seem rational in the asphyxial state were it readily available. Reports on its use, however, are not very enthusiastic (Doll, 1946), and it seems to be more effective in obstruction of the major air passages than in bronchiolar obstruction.

Summary

In a series of 100 admissions to hospital for status asthmaticus all were initially adrenalin resistant.

The important factors in their management have been environmental control, parenteral aminophyllin, and, where this fails, corticosteroids.

Forty-three of the 100 were controlled by aminophyllin, 51 needed steroids in addition, either ACTH or cortisone, with relief in 47. Three patients died, and the remainder were relieved by varying combinations of adrenalin, antibiotics and sedatives.

I must pay thanks to a succession of house physicians and registrars who have treated these asthmatics, and to my two ward sisters at the General Hospital who have cared for all these patients, many of them trying and difficult people, with such understanding and composure.

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ASSISTED RESPIRATION IN RESPIRATORY DISEASE

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The idea of blowing life into the apparently dead, as if rekindling a flame by blowing on the embers, seems to have been present throughout history. It was certainly evident in biblical times; the prophet Elisha, who revived the child of the Shunammite woman, could well have been an early exponent of the mouth-to-mouth resuscitation technique. One of the first recorded instances of an apparatus being used for artificial respiration concerns Paracelsus. In 1530 he is reputed to have used his fireside bellows for rhythmically inflating the lungs of apnœic patients after pressing the nozzle up their nostrils (Chaussier, 1785). This was effective when the bellows were not fouled with cinder grit. Woilley, a French physician, produced a breathing machine with cylinder and bellows in 1881 which was the forerunner of the cabinet type and intermittent positive pressure breathing apparatuses of today.

Until recent times, methods of artificial respiration have been mainly the concern of anæsthetists and first-aiders, though "iron lungs" were used in nursing occasional poliomyelitis patients, usually in special units. However, following the demonstration by Lassen and Ibsen, during the poliomyelitis epidemic of 1952, that patients could be maintained for prolonged periods with intermittent lung inflation through an endotracheal tube, the use of mechanical ventilatory assistance is becoming part of routine medical therapy.

Indications

There seem to be three main groups of patients with respiratory disease who may benefit from ventilatory assistance. First, there are those patients who are so critically ill with primary or secondary lung disease that depression of the respiratory centre is added to their difficulties; overwhelming influenzal or pneumonic disease in debilitated patients is an instance (DiMase *et al.*, 1959). Artificial respiration, perhaps combined with hypothermia, may tide them over the crisis by securing adequate oxygenation and reducing the work of the respiratory muscles. Secondly, there are the post-anæsthetic problems in patients with respiratory disease. These patients may have recurrent bouts of carbon dioxide narcosis, due to a combination of intrinsic lung disease and respiratory centre or neuromuscular depression, due to drugs. They benefit strikingly from an increase in ventilation. However, reaccumulation of carbon dioxide and rapid relapse into apnœa often follows the stopping of ventilatory assistance on apparently full recovery, and the treatment may have to be continued for some hours. It has been shown that in the post-operative period patients have, in general, a low arterial oxygen tension and that their respiratory work is increased (Linderholm and Norlander, 1955; Maloney and Whitten-

berger, 1950). The use of assisted ventilation for a time in post-operative patients with intrinsic lung disease and post-thoracotomy patients, to reduce the work and oxygen consumption of the respiratory muscles and to ensure adequate lung inflation, is rational and useful. Finally, there are the medical problems of pulmonary œdema, obstructive airway diseases such as chronic bronchitis, asthma and emphysema, and the hypoventilation syndromes.

Pulmonary œdema due to left ventricular failure is improved, sometimes dramatically, by positive pressure ventilation; that due to other causes may not respond. The probable mechanism lies in the obstruction to venous return consequent on the increased intrathoracic pressure. This acts like the application of tourniquets to the limbs. It is irrational to consider that an increase in alveolar pressure in some way prevents capillary exudation, since the balance of forces across the pulmonary vasculature is not altered by positive pressure ventilation, except in so far as the resting lung volume is increased (Maloney and Whittenberger, 1955). The main group, the patients with obstructive airway disease, are often admitted with anoxæmia and carbon dioxide retention secondary to a flare-up in their respiratory infection. They may present the picture of a cerebral tumour (Conn *et al.*, 1957) or psychiatric abnormality (Brown, 1930). Treatment in an oxygen tent removes the anoxic drive to respiration, and they hypoventilate or become completely apnœic with further defect in CO_2 elimination, increase in hypercapnia and, often, unconsciousness (Donald, 1949). Respiratory stimulants, such as the Diamox and aminophylline régime (Galdston and Hollis, 1957), may be effective in some cases, but the safest treatment is assisted ventilation. Carbon dioxide elimination is thereby assured and, perhaps more important, oxygen can be given in an adequate concentration. Simultaneous bronchodilator therapy seems to be useful. Cor pulmonale is not a contraindication and may be much improved by this therapy. It is unlikely that the maldistribution of inspired gas, which occurs in obstructive airway disease, is benefited by artificial ventilation. In fact, it is not likely that the pattern of lung expansion is ever normal without the active co-ordination of the respiratory muscles. The improvement is probably due to the correction of the underventilation which is always present, and the reduction in the excessive oxygen demands of the respiratory muscles (Fritts and Cournand, 1956). Syndromes associated with alveolar hypoventilation, anoxæmia, and eventual carbon dioxide retention, of which the most generally recognised is the Pickwickian syndrome, but which include most of the diseases causing chest wall weakness, deformity or restriction, are, of course, similarly helped by mechanical ventilatory assistance. Unfortunately many of these conditions are irreversible; but some (poliomyelitis, polyneuritis, myasthenia gravis, obesity, and the treatment of tetanus with muscle relaxants) may not require permanent respiratory assistance.

Methods

Most of the manual methods of artificial respiration were introduced after experiments on relaxed volunteers. It was not then appreciated that the relaxed

oro-pharynx so frequently prevents ventilation taking place, or that the lungs become stiffer (reduced compliance) after any period of reduced ventilation or apnœa. Indeed the pressure required to distend them in an unconscious patient with an airway in place may be more than twice that which is effective in the relaxed normal subject (Butler and Smith, 1957). The manual methods are generally incapable of achieving or maintaining adequate blood oxygenation in apnœic patients (Galdston and Hollis, 1957). Emergency resuscitation is best done by the mouth-to-mouth method, with the head extended and the hands holding the jaw forward. A tidal volume of about 1 litre at a rate of 12 to 20 BPM is effective and readily maintained. Obstruction can be easily sensed and many studies have confirmed that full blood oxygenation and carbon dioxide elimination are achieved (Dill, 1958). An oral airway or a hole in a handkerchief over the patient's mouth makes the procedure more acceptable (Dobkin, 1959).

Ventilation by pressure changes around the body, as in cabinet respirators, is effective when there is no problem of upper airway obstruction. It is equivalent to intermittent positive pressure ventilation as regards the pressure gradient produced between the intrathoracic and extrathoracic structures—the negative phase corresponding to the positive inflationary phase of pressure breathing—and no advantage can be expected from its use in states of shock. Disadvantages are the relative inaccessibility of the patient, the difficulty in maintaining the same degree of sealing at the neck and of monitoring tidal volumes, the possibility of regurgitation and inhalation of vomitus, and the ever-present danger of upper airway obstruction. Intermittent positive (I.P.P.) or positive/negative pressure ventilation seems to have less disadvantages and will be the basis of the present discussion.

It necessitates a high tracheotomy and the introduction of a cuffed endotracheal tube if it is to be used for more than the 24 or so hours that a laryngeal tube can be left in place. Tracheotomy itself may be very helpful in respiratory disease (Davidson, 1959). It is a minor operation and our own experience with it has been uniformly encouraging. It reduces respiratory work by abolishing upper airway resistance, since that of the tracheotomy tube should be very low. The dead space of the upper airway is by-passed, so smaller tidal volumes give the same alveolar ventilation. The bronchi may be sucked out and bronchodilator therapy applied through the tracheostome. These factors may be sufficient in themselves to reduce carbon dioxide retention in obstructive airway disease. Humidification of the inspired air is necessary for an open tracheotomy, or desiccation of mucosa and infection are likely. This can be achieved by passing air over warm water and into a cellophane mask hung loosely over the tracheotomy opening, or by the use of a simple metal baffle in the rebreathing tube as a heat and moisture exchanger (Koch *et al.*, 1958). In some patients with bronchiectasis a tracheal fenestration may be done, which allows normal speech and coughing, but provides a valved opening through which bronchial suction can be performed by the patient.

The schematic I.P.P. apparatus (Fig. 1) illustrates some of the important features in design. Air, or oxygen enriched gas mixtures if necessary, are

delivered by the pump through the endotracheal or laryngeal tube at a positive pressure which inflates the chest. Deflation occurs by passive recoil of the chest which may be aided by suction (negative phase) from the apparatus. It is theoretically desirable that the apparatus should deliver a preset volume, with a manometer registering the pressure at the mouth and a safety valve to prevent excess pressure being developed, rather than work from regulated delivery pressures. A relatively constant ventilation can then be achieved in spite of the changes in lung compliance and resistance which occur over short periods of time in these patients. Valves are necessary to prevent rebreathing. It is a big advantage if these are power-operated, since the sticking of moist rubber valves is a grave risk. The air should be passed through a humidifier or heat

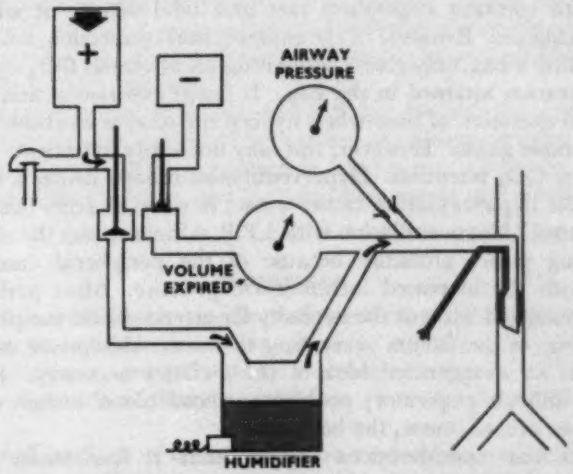

FIG. 1.—Diagram of intermittent positive/negative pressure apparatus. Inflation phase. Schematic trachea on right. The boxes (upper left) represent the bellows.

and moisture exchanger, close to the tracheotomy, so that it is saturated and at body temperature when delivered. The cuffed endotracheal tube must be as large as can be conveniently introduced; its frictional resistance is therefore low. If it is not fairly rigid, it may be squashed when the cuff is inflated. The cuff is usually let down every few hours to prevent ischæmic necrosis of the tracheal mucosa; and suction at these times is particularly important to prevent nasopharyngeal secretions running past into the bronchi. It is best to measure gas volumes expired, since much of the volume delivered may be lost in leakages and fail to ventilate the patient. Frequent bronchial aspirations, using sterile soft rubber catheters, and the administration of bronchodilator sprays, are important, particularly in bronchitic patients.

Initial hyperventilation, with reassurance and sedation, usually enables the machine to impose the required minute volumes in conscious patients without

difficulty. We have had little success in the use of patient-triggered devices in increasing minute volumes in respiratory disease. Triggering may be inadequate owing to depression of the respiratory centre, or too uneven because of lack of co-operation. They may have a place in the later stages of treatment. The minute volumes predicted from Radford's Nomogram (1954) are too low in patients with abnormalities in the relationship of ventilation to blood perfusion in different parts of the lungs. Hyperventilation, rather than the correct minute volumes, should be aimed for initially. When air is used as the inflating gas, the machine can be regulated so that it just keeps the colour of warm parts pink. CO_2 elimination is then ensured. Oxygen addition upsets this control. Sampling the CO_2 concentration in the expired gas at the end of expiration is not helpful in estimating blood gas tensions in patients with emphysema; however, with constant respiratory rate and tidal volume it will show the direction of changes. Removal of the endotracheal connection, and a period of rebreathing into a bag, may give a better estimate of venous CO_2 levels from the CO_2 concentration attained in the bag. It is our experience that an alkaline urine, due to excretion of base when hyperventilation is established, is a very useful and simple guide. However, this may not apply in patients who are not suffering from CO_2 retention. Hyperventilation usually causes a fall in blood pressure, while hypoventilation causes a rise; in some patients this allows very accurate control. Hypoventilation with I.P.P. seldom causes the classical flush and bounding pulse, probably because of the peripheral vasoconstriction associated with the increased intrathoracic pressure. Most patients can be adequately managed without the necessity for arterial blood sampling, and it is a pity that one of the factors preventing the more widespread use of assisted ventilation is an exaggerated idea of the facilities necessary. However, in following a difficult respiratory problem, arterial blood carbon dioxide and oxygen tension are, of course, the best guide.

Cardiovascular considerations suggest that a low mean intrapleural pressure should be aimed at, to lessen the obstruction to venous return. Thus a short, " square wave " of positive inflationary pressure with a long deflationary phase of atmospheric pressure at the mouth—one-third inspiration and two-thirds expiration—should be beneficial (Spalding, 1955). Only about half of the distending pressure at end-inspiration is normally transmitted to the intrapleural space; in patients with airway obstruction, a much lower proportion of the maximum mouth pressure (less than one-third, depending on the degree of obstruction) affects the intrapleural space during the inflationary phase (Barach *et al.*, 1947). The deflationary phase may be initiated by a negative phase at the mouth—the airways are then most widely dilated and the danger of their collapse is least—which further reduces the mean intrapleural pressure. Raising the foot of the bed increases venous return and cardiac output in patients having I.P.P. (Berneus *et al.*, 1954).

Ventilatory considerations suggest a completely different respiratory pattern (Butler, 1957a). A slow rate of inflation improves gas distribution (Otis *et al.*, 1956). Studies on anæsthetised patients emphasised the benefits of a high mean airway pressure in reducing airway resistance (Butler, 1957).

A negative phase in bronchitic patients caused an enormous increase in resistance and often stopped deflation. Bronchi may be seen by bronchography to collapse, with associated gas trapping, under these circumstances (Lynch *et al.*, 1959); once an airway closes it takes a greater pressure to reopen it. Again, the lungs are less rigid after expansion with large tidal volumes and become more rigid with positive/negative than with I.P.P. ventilation. It is, therefore, rational to limit the use of the negative phase mainly to patients with blood loss, shock or autonomic upset. In such patients who have obstructive airway disease, it is best used to initiate deflation rapidly when the lungs are distended. The use of positive epigastric pressure (pneumobelt)* at this time, in place of the negative phase, may have some advantages, particularly in view of reports of over-distension in emphysema treated by I.P.P. alone (Gray and Field, 1959). A large tidal volume should always be given now and then to prevent the increased lung rigidity, associated with apnœa or artificial ventilation, becoming irreversible.

It is disappointing to find that many of the patients successfully treated for their carbon dioxide retention by assisted ventilation return to the same state when their next respiratory infection takes place. However, some go for years without further trouble, and the treatment seems well worth while.

Summary

(1) Assisted ventilation may be indicated in overwhelming respiratory infections, in post-anæsthetic carbon dioxide retention and post-operative respiratory problems, in pulmonary œdema, obstructive airway disease associated with carbon dioxide retention, and in hypoventilation syndromes.

(2) Manual methods of resuscitation are inadequate and mouth-to-mouth ventilation is better. Cabinet respirators make nursing difficult. Intermittent positive pressure (I.P.P.) or positive/negative pressure ventilation through a tracheotomy tube is the method of choice. A tracheotomy alone may suffice in some patients.

(3) I.P.P. should be volume regulated. Mechanically operated rather than rubber valves are an advantage. A humidifier near the tracheostome is necessary and expired rather than inspired volumes should be monitored.

(4) Cardiovascular considerations suggest a rapid inflation followed by a prolonged expiratory interval at a negative airway pressure. Respiratory considerations stress a slow inflation with a higher mean airway pressure and the hazards of the negative phase. A negative phase is probably best used in patients with shock.

(5) Management does not necessarily require more than clinical judgment, airway pressure and minute volume readings, blood pressures and, perhaps, expired CO_2 analysis on occasions. Arterial blood gas tensions are only necessary in complicated situations.

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The Lungs and Heart Disease

PULMONARY HÆMODYNAMICS

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Professor Arnott has asked me to open the final session of this symposium by reviewing briefly the characteristics of the pulmonary circulation and its response to disease processes.

The pulmonary circulation differs greatly from the systemic circulation. It is a low resistance, low pressure and low compliance system. The cardiac output flows through it with a pressure gradient of less than 10 mm. Hg, its resistance to blood flow being less than one-eighth of that of the systemic circulation. The systemic circulation feeds many different organs with different functions and rapidly varying demands for blood. The structure and function of the whole of the lung is relatively uniform, being concerned with the adequate transfer of gases between air and blood. It is difficult to see why there should be any marked vasometric changes to increase the pulmonary vascular resistance or alter the regional distribution in healthy lungs.

Pressure-Flow Relationships and Pulmonary Vascular Resistance

Let us first consider the pressure-flow relationships in health. The mean pulmonary arterial pressure is of the order of 12-20 mm. Hg, the pulmonary venous and left atrial pressure of the order of 7-12 mm. Hg. The latter figure has been directly determined in human subjects by needling from the bronchus and through the chest wall. The values obtained are in remarkable concordance with those obtained when a cardiac catheter is wedged into a branch of the pulmonary artery. It was thought at first that the pressure obtained in this way was probably representative of the pulmonary capillary pressure. However, it is now known that there is little anastomosis, except under extreme experimental conditions, between different parts of the lung circulation at this level of division. Blood flow ceases in the segment of lung whose vessel is impacted, and the pressure throughout the arteries, arterioles, capillaries and veins of the segment will be uniform and equal to that in the pulmonary veins where there is normal flow of blood. In other words, the vessels of the impacted lung segment will act as an imperfect but somewhat bizarre extension to the catheter which transmits the pressure in the veins of the unobstructed pulmonary segments. This would explain why the "wedge pressure" tracings give a mean pressure very close to the left atrial pressure, although the wave characteristics are variably and unpredictably modified by the vasculature of the impacted segment. We thus have the situation in which the outflow pressure of the lungs is being measured by a catheter from the inflow side. This remains to me one of the most remarkable examples of human ingenuity in

investigative work, and if anyone states that a desired parameter is inaccessible in the intact human subject, I now reserve judgment.

On exercise the outflow pressure alters but little. The inflow or pulmonary arterial pressure rises slightly in the normal subject but, speaking generally, the calculated resistance of the lung vasculature remains unchanged.

The calculation of the vascular resistance involves essentially the determination of the pressure gradient across the lung vasculature (pulmonary artery to pulmonary veins) per unit of blood flow. However, both inflow and outflow pressures are pulsatile and both pulse and mean pressures and the inflow and outflow of blood are all separately and differently affected by respiration. Further, as we will see later, flow is pulsatile down to the capillary bed. Thus the use of the mean difference between mean inflow and outflow pressures and of a mean flow in the calculation of the mean resistance will involve considerable errors. Further, energy expended on the distension of lung vessels and movement of soft tissues is at present included in the calculation of resistance and not assessed separately. Nevertheless, despite these imperfections, the relationship of pressure to flow is essential in the estimation of vascular resistance. Further, records of the mean pressure difference on a differential manometer during apnœa at the resting respiratory level resolve the difficulties due to respiration.

While considering the pulmonary vascular resistance it is worth briefly reviewing the anatomy of the pulmonary circulation. The pulmonary artery is capacious, with thin but highly elastic walls. This elastic wall is continued until the branches are about 1,000 μ in diameter. A definite muscular coat is then found which continues until the calibre is of the order of 100 μ. After this the arteries have a very thin elastic wall and are almost indistinguishable from the small veins leaving the pulmonary capillaries. Thus the arterioles of the lung are not capable of vasometric activity, but only a limited length of the smaller branches of the pulmonary artery. The capillaries are a generous mesh in the walls of the alveoli and the circulatory blood is as near to a continuous sheet as structural factors will allow.

The pulmonary vascular bed is also capable of sudden changes in volume with very small changes in pressure. This reservoir action of the lung circulation has long been taught but only poorly studied. It is estimated that the volume of blood in the lung vessels of an average-sized man is about 1 litre and that on lying down it is increased by about 300 ml. Carbon monoxide studies suggest that the volume of blood in the capillaries exposed to lung gases is only of the order of 60 ml. The pulmonary arteries are only moderately distensible, the capillaries even less, and it is considered that the main reservoirs involved in sudden changes of volume are the pulmonary veins.

Owing to the relatively low resistance of the pulmonary arterial tree the pulmonary capillaries exhibit considerable pulsation. This has been demonstrated directly by biomicroscopy in animals and indirectly in human subjects by the change of rate of uptake of nitrous oxide (a measure of blood flow) during the heart cycle. The uptake of nitrous oxide and capillary blood flow may fall to almost zero late in diastole.

Vasomotricity of the Pulmonary Vascular Bed

One of the major preoccupations of respiratory and circulatory physiologists during the last twenty years has been the problem of local, autonomous and central control of blood circulation through the various parts of the lungs. The fact that this problem is but little resolved would suggest that we are dealing with mechanisms of great subtlety or of only vestigial significance. A few facts are reasonably established. Both the pulmonary arteries and veins have pressure receptors in great profusion, and afferent vagal impulses synchronous with pulsatile changes in the pulmonary circulation but independent of systemic pressure changes have been demonstrated.

Generalised alveolar hypoxia causes a rise in the pulmonary vascular resistance of a very moderate order. This increase has been shown to be independent of the main nerve supply of the lungs and is unaffected by blood oxygen tensions within the pulmonary circulation itself. Although a local alveolar-pulmonary artery axon reflex is a remote possibility there is no evidence of this and it is not unlikely that the increase of vascular resistance is due to a direct metabolic effect on the cells of the pulmonary capillaries. If the general alveolar hypoxia becomes extreme, then the resistance will fall again and this would appear to be in the interests of the organism. This may be due to the increased tone of the capillary wall being lost owing to enzymatic dysfunction at these very low levels of oxygenation.

The reduction of blood flow to areas of poor alveolar ventilation or of low alveolar oxygen tensions has been demonstrated in both animals and man and this would appear to be advantageous to the organism if there are minor pulmonary disturbances interfering with alveolar ventilation. Acetylcholine, when injected into the pulmonary circulation in sufficiently small doses to avoid systemic effects, causes a fall in pulmonary vascular resistance in both animals and man, particularly if the resistance is abnormally raised by experimental (hypoxia) or pathological factors. Again this action is thought to be highly local and not mediated by any neural mechanisms. Ganglion-blocking agents also cause a fall in resistance, but their action is very variable. This is not surprising in view of their widespread action throughout the body.

It has been recently shown in animals that a rise of systemic blood pressure causes a fall in pulmonary vascular resistance, and a fall of systemic blood pressure, a rise. This reflex can be eliminated by denervating the carotid sinus. If I may be allowed to speculate, this reflex may be in order to shift blood from the major arterial system to the lungs when the arterial pressure rises. A fall of pulmonary vascular resistance and presumably of vessel tone may allow such a shift. Finally, the criteria for significant experiments involving changes of the pulmonary vascular resistance have become very severe. One should be able to demonstrate that there have been no simultaneous alterations of lung mechanics (particularly affecting alveolar or intrapleural pressures), of pulmonary blood volume, of outflow pressure, or that any secondary effects have been caused by changes in the systemic or bronchial circulation. Even the most experienced worker must be daunted by such demands.

Diffusing Capacity

The diffusing capacity of the lungs has already been discussed in considerable detail. I would, however, like to mention briefly the relation of the pulmonary circulation to the diffusing capacity. The diffusing capacity (D_L) as usually measured has two important components: the first concerns the transfer of oxygen through the structures intervening between the alveolar gas and the pulmonary blood (D_M), the second the accessibility of reduced hæmoglobin and the finite rate of combination of the gas with hæmoglobin. If these structures or factors are considered as serial impedances to the passage of oxygen from the alveolus to the hæmoglobin molecule, then the impedance of the alveolo-capillary membrane is approximately of the same order as the impedance due to plasma, red cell envelope and fluid and the finite rate of combinations of oxygen and hæmoglobin.

The true diffusing capacity of the lung is a function of the surface area of lung capillaries in contact with ventilated alveoli. This again will be affected by the number of capillaries being perfused at that time and the degree of distension of these capillaries. The more the capillaries are distended the greater and thinner will be the effective alveolo-capillary membrane. The intra-capillary impedance factors depend on the accessibility of reduced hæmoglobin and this is mainly a function of capillary blood volume, the hæmatocrit and mixed venous blood oxygen saturation. The velocity of the reaction between oxygen and reduced hæmoglobin also varies with the oxygen tension and is greater at lower tensions.

It is estimated that the apparent diffusing capacity at rest, as measured by the classical two-level oxygen or carbon monoxide technique, is about half (twice the impedance) of the true diffusing capacity of the alveolo-capillary membrane.

On exercise the apparent diffusing capacity can increase four- or five-fold. This rise occurs almost synchronously with the exercise in increase in cardiac output and pulmonary blood flow. With the increase in flow the volume of blood in the pulmonary capillaries increases from a resting value of 80 ml. to values up to 170 ml. (average-sized man). This increase in volume will increase the diffusing capacity by the increase in the area of the alveolo-capillary membrane as already discussed. It is also possible that capillaries which were collapsed at rest are opened up on exercise, and this would cause a considerable increase of diffusing capacity. There is however no definite evidence that pulmonary capillaries behave in this manner. However, recent studies have shown that the largest part of the increase of the apparent diffusing capacity is due to the reduction of the intracapillary impedance to the combination of oxygen and hæmoglobin. This is due to several factors. Firstly, the increased capillary volume makes more hæmoglobin available; secondly, the proportion of reduced hæmoglobin present is abruptly increased with exercise; thirdly, the hæmatocrit rises with exercise; and, fourthly, the considerably reduced oxygen tension in the " proximal " capillary causes an increase in the rate of combination of oxygen and reduced hæmoglobin. Summarising, the increase in oxygen transfer (per unit of gas tension gradient) is certainly due in part to

changes in the wall characteristics of the pulmonary capillary blood, but the greatest part of the increase is due to the behaviour of the blood and not of the lungs.

Lung Diseases

Let us now consider the changes in pulmonary blood flow, pressures and diffusing capacity in common lung diseases.

In the large majority of patients with moderate to severe pulmonary emphysema the right heart does not show signs of embarrassment or hypertrophy, even in the presence of considerable ventilatory disability. The "small vertical" heart of these patients is well known in clinical medicine. The cardiac output is normal at rest and on exercise (which is often limited by ventilating discomfort). The pulmonary arterial pressure is but little raised at rest (30 mm. Hg approximately). It is thought that this slight rise in pulmonary vascular resistance is due to an actual reduction of the vascular bed. Yet, considering the apparently highly abnormal injection studies found after death in the disease and the damaged and poorly vascularised alveoli seen in histological studies, the rise of resistance is remarkably small. The distension of the lung and air trapping before and even after death may empty alveoli of blood and give a very false impression of the degree of vascular damage.

On exercise the pulmonary arterial pressure is again abnormally elevated, but rarely to the levels encountered in other diseases.

The diffusing capacity is low in the presence of severe emphysema. This is because the effective blood gas interface is greatly reduced by the lack of adequate ventilation of considerable areas of lung and also by the reduction of perfusion of others. The diffusing capacity remains low on exercise and it is this feature which causes severe arterial blood desaturation rather than a further increase in gas distributional disturbances. It is possible, and indeed probable, that the alveolar capillary bed which is adequately ventilated has a relatively high blood flow and near maximum capillary blood volume. Thus the normal reserves for increase of diffusing capacity on exercise are no longer available.

When patients with severe emphysema develop acute respiratory infections, then a considerable proportion of the already reduced functioning lung is no longer ventilated adequately. Acute and severe pulmonary insufficiency occurs and dangerous hypoxæmia and hypercarbia result. These and the fever will cause widespread systemic vasodilatation and in order to maintain the systemic blood pressure the cardiac output is raised. The pulmonary arterial pressure also rises abruptly to moderately high levels and this is usually considered to be due to marked alveolar hypoxia causing an increase in pulmonary vascular resistance. Yet this pulmonary hypertension is rarely reduced to any extent by the administration of oxygen and the rise is of a far greater order than is usually caused by experimentally induced low alveolar oxygen tensions. It is more likely that much of the increase of resistance is of mechanical rather than vasometric origin. The trapping of air on expiration in previously functioning lung must cause high positive alveolar pressures and capillary collapse, and this and actual cessation of flow through collapsed or pneumonic

areas may well be the main causes of the increased pulmonary arterial pressure.

No matter what the causes, the sudden rise of pulmonary vascular resistance and of cardiac output in the face of severe hypoxæmia precipitate right ventricular failure in these patients. It is probable that a perfectly normal healthy right ventricle would fail under such conditions.

In diffuse pulmonary fibrosis (usually industrial in origin) the pulmonary vascular resistance may be normal or only slightly raised at rest or on exercise, in the presence of marked radiological changes, but in the absence of any significant arterial blood desaturation. Again, it is likely that this rise is due to mechanical factors. The diffusing capacity is not markedly impaired. Later in the disease there may be a more marked rise of pulmonary vascular resistance and fall of diffusing capacity, particularly with the intervention of massive fibrosis, lung destruction and parenchymal degeneration of the remaining lung.

The patho-physiology in conditions with so-called "alveolo-capillary block" has already been discussed. The pulmonary vascular resistance may become greatly raised even in the presence of normal resting arterial blood saturation, and this is probably due to mechanical interference with the circulation, perhaps largely at the capillary level. Although increased impedance to the passage of oxygen through the alveolo-capillary membrane is the conspicuous feature in this disease, studies of ventilation-perfusion relationship suggest that obstruction of capillary vessels also plays an important role. The increase of pulmonary vascular resistance often progresses unremittingly and death from right ventricular failure is not uncommon, even when the patient is maintained at normal levels of oxygenation by oxygen therapy.

In conditions such as tuberculosis (massive healing) or bronchiectasis the pulmonary vascular resistance and pulmonary arterial pressures remain normal in the presence of remarkably widespread radiographic abnormalities. The actual volume of lung parenchyma involved is usually far less than is judged by a summation of radiological shadows in one view. If, however, bronchitis and emphysema supervene, then pulmonary hypertension may develop with surprising rapidity.

Mitral Stenosis

I would not like to finish this short review without discussing one example of the pulmonary circulation and lung function in heart disease, namely mitral stenosis.

In this condition with increasing mitral valve obstruction there is a rise of pressure in the left atrium and the whole of the pulmonary vasculature. If this "back pressure" exceeds 35 mm. Hg, then pulmonary œdema will develop. However, this rarely occurs except during exercise in young and apparently fit patients. This is because atrial fibrillation and other factors we do not understand cause a fall of cardiac output and a life-saving reduction of the gradient across the stenosed valve. The main cause of the great increase in pulmonary arterial pressure found in many of these patients is an increase in the pulmonary vascular resistance which is an added and little understood phenomenon.

Reverting to pulmonary function, it is remarkable how efficiently blood oxygenation is performed by the lungs, despite the raised vascular pressures. There are several factors which help. There is increased ventilation which will combat any poor gas distribution. The low cardiac output causes the mixed venous blood oxygen tension to be very low with a further increase of the initial alveolo-capillary oxygen tension gradient. The low rate of blood flow through the lungs is also favourable to gas transfer.

Special tests do, however, show varying degrees of disturbance of the ventilation-perfusion relationships and, on some occasions, a reduction of diffusing capacity. The frequent occurrence of bronchitis in such patients is a complicating factor, but there is no doubt that these changes can occur in its absence. One would expect the increased pressure in the pulmonary capillaries to result in a permanently raised intra-capillary volume and diffusing capacity (both apparent and real). Yet this has not been reported. This may be due to decreased compliance of the lungs. Increasingly negative intrathoracic (and endovascular) pressures are necessary during respiration and this may have a collapsing effect on the capillaries which are exposed to atmospheric and near-atmospheric pressures. It is possible that the decrease of compliance is more marked at the lung bases with resultant regional underventilation. The circulation through the lower parts of the lungs may be reduced because of hypoxic vasoconstriction and capillary collapse. This reduction of effectively ventilated and circulated lung would explain many mysterious features of respiratory physiology in heart disease, particularly the increased ventilation. These theoretical considerations have been supported by recent work using radioactive oxygen and carbon dioxide. These have shown that, whereas in the upright normal subject the upper lobes receive far less blood than the lower owing to gravity, this difference may disappear, or even be reversed, in patients with mitral stenosis. The ventilation of the lower lobes does not however appear to be greatly reduced and much more work is needed to determine the causes of this phenomenon.

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PATHOLOGY OF THE PULMONARY VESSELS

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Characteristic structural changes occur in the elastic and muscular arteries and the arterioles of the lung in patients with chronic pulmonary hypertension.

Elastic Pulmonary Arteries

The appearances of the elastic tissue of the fœtal pulmonary trunk are similar to those of the aorta, although minor differences are present. In both there are many long, uniform elastic fibrils, tightly packed and circularly arranged, among fibrous tissue and smooth muscle which is orientated similarly. The elastic tissue remains in this form in the adult aorta, but fragmentation of the fibres of the pulmonary trunk occurs in infancy, so that the appearance of the elastica of this vessel in the adult is that of a loosely arranged network of branching, irregularly shaped, fragmented fibrils. In severe pulmonary hypertension the media of the pulmonary trunk increases in thickness in all instances, but the appearance of the elastic tissue depends upon the time of onset of the elevation of blood pressure in the pulmonary circulation (Heath *et al.*, 1959). In the presence of a large ventricular septal defect or a widely patent ductus arteriosus the pulmonary hypertension exists from birth and the media of the pulmonary trunk retains the fœtal, aorta-like configuration of elastic tissue. Diseases such as atrial septal defect and rheumatic mitral stenosis lead to the development of pulmonary hypertension later in life, and by this time the elastic tissue has undergone the normal transition to the open adult form.

In severe pulmonary hypertension there is severe atherosclerosis of the elastic pulmonary arteries. Cystic medial necrosis also develops and may predispose to rupture of one of the major pulmonary vessels.

Progressive histological changes also develop in the media and intima of muscular pulmonary arteries and arterioles in the presence of a chronic elevation of pulmonary artery blood pressure complicating congenital septal defects. Heath and Edwards (1958) have shown that this progression is so stereotyped as to allow a division of the structural effects of the hypertension into six grades. Their classification was based on the study of lungs from 67 patients having congenital heart disease and 2 having idiopathic pulmonary hypertension.

Grade 1. In ventricular septal defect and widely patent ductus arteriosus there is increased medial thickness in muscular pulmonary arteries and pulmonary arterioles. The normal muscular pulmonary artery is a vessel of between 100 and 1,000 μ in diameter with a media of smooth muscle bound between internal and external elastic laminæ. The medial thickness is equivalent to 5 per cent. or less of the external diameter of the artery. When there is chronic pulmonary hypertension this thickness increases to as much as 30 per

cent. of the diameter and is brought about mainly by the development of circularly arranged smooth muscle fibres. Longitudinal muscle may also develop beneath the external elastic lamina and some of the apparent medial hypertrophy may be accounted for by vasoconstriction. The normal pulmonary arteriole is 100 μ or less in diameter and comprises a single elastic lamina and a lining of endothelium. In pulmonary hypertension, however, the arteriole has a thick muscular media like that of the fœtal pulmonary artery of comparable diameter, the intralobular artery. Such retention of thick-walled, fœtal-like pulmonary arteries, when an elevated pulmonary-artery blood-pressure has been present from birth, is analogous to the retention of the fœtal, aorta-like arrangement of elastic tissue in the pulmonary trunk subjected to similar hæmodynamic abnormalities. Like the myocardium of the right ventricle, the muscle of the media of the elastic and muscular pulmonary arteries and of the pulmonary arteriole becomes hypertrophied in severe chronic pulmonary hypertension.

The earliest pulmonary vascular changes seen in atrial septal defect differ from those described in that cellular intimal proliferation in the pulmonary arterioles and the smallest muscular pulmonary arteries precede the formation of a muscular media in the pulmonary arteriole. The normal transition to the thin-walled pulmonary arteriole in atrial septal defect occurs in infancy.

Grade 2. In atrial septal defect medial hypertrophy occurs in this grade, whereas in ventricular septal defect there is cellular intimal proliferation in the small pulmonary blood vessels. Hence from grade 2 onwards the progressive structural changes which develop in the pulmonary vasculature as a result of chronic pulmonary hypertension are identical.

Grade 3. The intimal proliferation which occurs in association with medial hypertrophy becomes fibrous and finally fibroelastic with elastosis of the internal elastic membrane. The intimal changes occur first in the pulmonary arterioles and the smallest muscular pulmonary arteries and progress until there is complete vascular occlusion. Often a small endothelium-lined central channel remains. The larger muscular pulmonary arteries rarely show intimal fibrosis.

Grade 4. With the passage of time and the exaggeration of the elevation of pulmonary resistance by the occlusive intimal lesions, extensive dilatation of the pulmonary arteries and arterioles occurs, with thinning of the media. There is fibrosis of the media as well as the intima.

Dilatation Lesions

At this stage, in addition to the generalised dilatation, excessive localised distension of vessels occurs at the sites where the muscular pulmonary arterioles give rise to arterioles. These sites are proximal in the pulmonary vascular tree as side branches of medium-sized muscular pulmonary arteries and distal as terminations of small muscular arteries. These complex "dilatation lesions" are pathognomonic of severe chronic pulmonary arterial hypertension and assume four main forms.

1. Arteriolar vein-like branches of occluded arteries. The arteriolar

branches of a hypertrophied muscular pulmonary artery may dilate proximal to the site of fibrolic occlusion of the artery to form vessels resembling veins. These cluster around the parent artery before passing to the lung substance to form alveolar capillaries.

2. The plexiform lesion. The branch dilates excessively to form a sac, and plexiform masses of proliferated endothelium may form in the sac, together with thrombus. The cellular material merges proximally in the sac with intimal fibrous tissue in the parent muscular pulmonary artery. It eventually fibroses.

3. The angiomatoid lesion. Dilated thin-walled branches cluster in the lung substance to form an angiomatoid mass giving rise to thin-walled vessels which eventually form capillaries in the alveolar walls.

4. The cavernous lesion. The dilated branches form cavernous spaces in the lung.

Grade 5. The lung becomes highly vascular on account of these numerous vein-like arterial branches which rupture and give rise to pulmonary hæmosiderosis.

Grade 6. Rarely acute or subacute necrotising arteritis occurs as a result of unusually severe pulmonary hypertension. This process begins around the sites where both intimal proliferation and dilatation lesions occur first, namely, at the junction of the muscular pulmonary artery and the pulmonary arteriole. There is necrosis of muscle and this stimulates an acute inflammatory reaction which is followed by healing and replacement of the dead tissue by masses of granulation tissue in the intima, media and adventitia.

The results of cardiac catheterisation have been correlated with the structural changes present in the lung, graded according to the above system, in 15 cases of atrial septal defect, 19 cases of ventricular septal defect and 6 cases of patent ductus arteriosus (Heath *et al.*, 1958a). The correlation shows that the grading system is valid as an estimate of those factors which determine the type of resistance to flow through the pulmonary vascular bed, if it is realised that in the very young the normal pulmonary bed has a high resistance. Grades 1 to 3 indicate a vascular bed which, though it may maintain a moderately high resistance, is labile. Grades 5 and 6 indicate a vascular bed that maintains a high resistance and that is no longer labile. Grade 4 represents a transitional stage between these two types of vascular bed.

The grade of hypertensive pulmonary vascular disease has also been related to the immediate change in pulmonary artery blood pressure following closure of a defect in the ventricular or atrial septum in each of 32 patients with congenital heart disease (Heath *et al.*, 1958b). In 23 of the 24 cases with grade 1 to 3 lesions the pulmonary hypertension was largely immediately reversible, the residual systolic blood pressure in the lesser circulation being less than 50 mm. Hg. In all 4 cases with grade 5 lesions the pulmonary hypertension was unchanged immediately after repair of the defect and the residual systolic blood pressures in the lesser circulation exceeded 50 mm. Hg. In 3 of the 4 cases of early dilatation of pulmonary arteries (grade 4) the pulmonary hypertension was partially reversible and in the fourth it was irreversible. In all 4 cases in this subgroup there was a residual systolic blood pressure in the lesser

circulation exceeding 50 mm. Hg. These data suggest that pulmonary vascular resistance and associated hypertension are composed of functional and organic components, the latter becoming increasingly important as the changes of hypertensive pulmonary vascular disease become more severe.

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FUNCTIONAL ASPECTS OF THE COR PULMONALE SYNDROME

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Cor pulmonale may be defined as disturbed function of the heart and circulation which arises from disease of the lungs and pulmonary vascular bed. In the final analysis this disturbance stems from two main causes, acting singly or in combination.

Firstly, there is failure to maintain the normal oxygen and CO_2 tensions of the arterial blood supplied to the tissues. This failure may be due to inadequate alveolar ventilation as in emphysema, to alveolar capillary block as in the so-called pulmonary fibroses, to intrapulmonary shunts such as occur in severe pulmonary vascular obliteration, or to intracardiac shunts as in the Eisenmenger syndrome of congenital cardiac defects.

Hypoxia with reduction of the oxygen tension and saturation of the arterial blood is common to them all. Retention of CO_2, hypercarbia, is associated when inadequate alveolar ventilation is the dominant disturbance. If the fault lies elsewhere hypoxic stimulation of respiration through the carotid sinus reflex induces alveolar hyperventilation and leads to a reduction of the arterial CO_2 tension, or hypocarbia.

When arterial hypoxia is severe, changes in systemic vasomotor tone, similar to those occurring in severe anæmia, will increase the cardiac output above the normal resting level and so produce a high-output or hyperkinetic state. Hypoxia stimulates the bone marrow to greater erythrocyte production and the total blood volume, hæmatocrit and blood viscosity are increased.

The second main cause of the cor pulmonale syndrome is an increase in the resistance to the flow of blood through the lungs. Again, this may arise in a variety of ways. The pulmonary vascular bed may be greatly reduced by extensive involvement in diffuse parenchymatous disease; when this is the only factor operating death from respiratory failure usually precedes any disabling increase in the vascular resistance. The pulmonary resistance may be increased by simple mechanical obstruction, thrombo-embolism from within or pressure from without. The most important cause of a high vascular resistance is an increase in the vaso-motor tone of the pulmonary arterioles. The factors which initiate this change are not fully understood. Local increases in tone occur and are probably compensatory, initiated by local decrease in alveolar oxygen tension, and so reducing perfusions to areas of the lung which are inadequately ventilated. Generalised pulmonary vasoconstriction is present from birth in those children who survive with large congenital defects and it thus provides a compensatory limitation of the left-to-right shunt which would be too large for life if the resistance fell to normal levels. Generalised increase in tone which occurs in later life is usually a response to passive pulmonary venous congestion

of chronic left heart failure. There remains a small group of cases, the so-called idiopathic pulmonary hypertensives, in which the initiating cause is still unknown. Whatever the trigger, continued pulmonary vasoconstriction is followed ultimately by irreversible organic changes which have been fully described by Dr. Heath, and which lead to a progressive obliteration of the vascular bed.

The cor pulmonale syndrome therefore presents as a variable combination of respiratory failure and increased pulmonary resistance. In any given case the relative importance of each depends upon the primary disease, its duration and associated complications. At one end of the scale, in rapidly progressive alveolar-capillary block, death occurs from respiratory failure. At the other end, in acute pulmonary embolism, death results from right ventricular failure.

Cor Pulmonale Heart Failure

The amount of work which the right ventricle can efficiently perform without failure depends upon the degree of compensatory hypertrophy. This is not a limitless process because it takes place by increase in size of the individual fibres which ultimately outgrow the most efficient blood supply and suffer ischæmic fibrosis in consequence.

Opportunities for adaptive hypertrophy depend upon the mode of development of the increased resistance to flow. These will be least in acute embolic obliteration of a normal bed and sudden right ventricular failure will follow. Adaptive hypertrophy is greatest in the Eisenmenger syndrome where the high resistance of the fœtal circulation has prepared the right ventricle for the abnormal work-load which it will carry from birth and which it usually sustains without difficulty for three or four decades of active life.

The severity of the pulmonary hypertension which precedes ventricular failure is therefore related to the degree of hypertrophy and this is determined by the duration of the increased vascular resistance and its rate of development.

Congestive heart failure occurs when the cardiac output is insufficient to meet the metabolic needs of the tissues. The level of flow at which this occurs is not constant from case to case or in the same individual at different times because it is determined by differing metabolic needs and hæmodynamic states. Thus, in emphysema cor pulmonale, the fever of infection, hypoxia and hypercarbia induce a high output state in which failure occurs with a resting output which may be 50 per cent. above normal. Contrarywise, embolic cor pulmonale in a patient at bed-rest may reduce output to half-normal before failure occurs. Nevertheless, whatever the level of output, this will be virtually fixed for, by definition, failure has occurred when the heart can no longer respond to increased demand by increased output. The renal blood flow will be greatly reduced, the ventricular filling pressure abnormally high and salt and water will be retained to produce the characteristic clinical picture of congestive failure.

Although several factors have been implicated the precise mechanism of cardiac œdema remains obscure. A disproportionate reduction of the renal

blood flow which results from the inadequate cardiac output will greatly decrease the tubular load of both sodium and water. Stimulation of " volume receptors " as a result of redistribution of blood within the vascular bed and loss of fluid into the extracellular compartment both resulting from an increase in the central venous pressure leads to increased production of sodium retaining steroids which act upon the renal tubules. Tissue hypoxia disturbs the normal intracellular balance of electrolytes and fluid, causing secondary tubular dysfunction. In emphysema cor pulmonale a fourth mechanism has been suggested, namely the retention of sodium base to compensate the severe respiratory acidosis.

The course of cor pulmonale heart failure depends largely upon whether the precipitating cause or causes are reversible. In acute cor pulmonale of embolism resolution of the clot and return of resistance to normal results in complete recovery. When, however, failure is due to progressive obliterative changes in the pulmonary arterioles grafted on to long-standing vaso-constriction, as in the Eisenmenger syndrome, the condition is irreversible and the course progressively downhill. It follows, therefore, that the greater the degree of right ventricular hypertrophy when failure comes, the worse the prognosis.

A triple rhythm audible over the right ventricle is a common early sign of the increased filling pressure which heralds failure. This will be accompanied or quickly followed by elevation of the jugular venous pulse. This pulse usually presents with the dominant V wave of increased filling pressure, but the form may be modified in two ways. Firstly, with gross right ventricular hypertrophy, secondary hypertrophy of the atrium may cause a giant atrial systolic wave visible and often palpable in the neck. Secondly, gross dilatation of the ventricle may be followed by functional tricupsid incompetence and the V wave is then replaced by a large wave synchronous with ventricular systole. When pulmonary hypertension is severe, functional incompetence of the pulmonary valve will produce the Graham Steele murmur. These functional valvular lesions add to the work of the failing ventricle and prejudice its recovery.

Emphysema Cor Pulmonale

In the quiescent phase of uncomplicated emphysema the clinical picture is dominated by ventilatory insufficiency. The arterial oxygen saturation is but slightly depressed and the arterial CO_2 normal. The pulmonary vascular resistance, although increased, causes little elevation of the pulmonary artery pressure and the right ventricular function is normal. This picture is greatly altered by infection. Alveolar ventilation and arterial oxygen saturation are profoundly depressed and retention of CO_2 occurs. This hypercarbia decreases the sensitivity of the respiratory centre and respiration, now mainly dependent upon hypoxic stimulation of the carotid sinus, is further depressed. This asphyxial condition, together with the fever of infection, causes a high cardiac output or hyperkinetic state. Widespread atelectasis and local increases in pulmonary vascular tone induced by alveolar hypoxia further increase the pulmonary vascular resistance. The right ventricle has to provide an increased

output against increased resistance with its oxygen supply diminished by hypoxia and without time for compensatory hypertrophy.

With a fulminating infection respiratory failure may come so rapidly that death from hypoxic circulatory failure occurs before the full picture of cor pulmonale heart failure has time to develop. When the infection is less severe congestive failure usually develops insidiously during the second or third week of the illness. Control of the infection and adequate oxygenation, coupled with relief of the œdema, will reverse this process and complete recovery from heart failure is the rule with a first attack. However, each fresh infection adds to the amount of permanent structural damage to the lungs and heart failure is more readily produced. If the course is long enough pulmonary hypertension may be permanently established and death from chronic right heart failure will follow.

Thrombo-embolic Cor Pulmonale

Obliteration of the effective vascular lumen by at least 65 per cent. is necessary before the right heart is embarrassed and it is, therefore, possible to have complete asymptomatic obstruction of blood flow to either lung. The clinical picture depends upon the rate at which the obstruction occurs and its degree. Small emboli giving rise to local areas of infarction with pain and hæmoptysis may give valuable evidence of what is occurring, but they are often absent and do not play an essential part in the functional disturbance which follows.

A sudden massive embolus causes acute right heart failure with circulatory collapse, hypotension, syncope, tachypnœa and tachycardia. In elderly patients with pre-existing coronary disease the hypotension may induce true ischæmic heart pain which confuses the diagnosis. Obstruction which exceeds 85 per cent. of the effective lumen causes death; with less the picture is one of acute right heart failure. Recovery is dependent upon the capacity of the right ventricle to maintain adequate forward flow until the obstruction is relieved by resolution, organisation and recanalisation of the clot.

Progressive silent embolisation presents insidiously with increasing exertional dyspnœa and cyanosis for which there is no apparent cause on clinical examination. These cases are sometimes dismissed as " hysterical " until frank right heart failure occurs, and are even then often mis-diagnosed as idiopathic pulmonary hypertension. The demonstration of past or present phlebothrombosis may be a valuable pointer to the true diagnosis. When the obstruction affects predominantly one lung, gross inequality of perfusion with normal ventilation, demonstrated by angiocardiography or bronchospirometry, will establish the diagnosis.

Although thrombo-embolic obliteration is now recognised as one of the primary causes of cor pulmonale, it occurs with much greater frequency as a complication of pre-existing pulmonary vascular disease. Low output failure encourages phlebo-thrombosis and pulmonary atherosclerosis favours the development of thrombosis *in situ*. Moreover, a high pulmonary resistance

enhances the effect of further obstruction and an embolism which could occlude a normal bed without signs or symptoms may cause death. It is for these reasons that thrombo-embolism plays such an important part in the terminal stages of all forms of cor pulmonale.

Primary Pulmonary Vascular Disease

Pulmonary hypertension which arises from a generalised increase in the tone of the pulmonary arteroles is consistent with reasonable cardio-respiratory function for many years. The increased work is met by ventricular hypertrophy. Although lung compliance may be reduced, ventilation and gas exchange are not seriously disturbed unless the condition has been provoked by passive pulmonary congestion. Deterioration occurs when the vascular resistance is further increased by superimposed irreversible obliterative disease. When this happens in patients with a ventricular septal defect or patent ductus arteriosus, the pre-existing balance between pulmonary and systemic vascular resistances is disturbed and the shunt which before was left-to-right or balanced becomes wholly right-to-left. The effective pulmonary blood flow falls progressively and central cyanosis with secondary polycythæmia occurs. These congenital abnormalities provide a useful safety valve for the right ventricle, allowing it to maintain adequate forward flow without increased work in spite of a rising pulmonary vascular resistance.

With atrial septal defect, on the other hand, the direction of the shunt is mainly determined by the relative filling pressures of the two ventricles, and a wholly right-to-left shunt in these cases signifies an abnormally high right ventricular filling pressure.

When no defect exists, adequate forward flow is wholly dependent upon the capacity of the right ventricle to meet and overcome the mounting vascular resistance. Damage to the pulmonary bed from the effect of high pressure will occur more commonly here and heart failure will take a rapidly downhill course. Occasionally central cyanosis with arterial oxygen unsaturation unrelieved by oxygen inhalation is met in the terminal stages of this condition and is due to the development of intra-pulmonary shunts through the plexiform and dilatation lesions which have been described by Dr. Heath.

The pattern of heart failure in mitral stenosis is outside the scope of this paper. Suffice it to say that in a proportion of these cases the reactive increase in pulmonary vascular resistance may be so great that they resemble clinically cor pulmonale due to primary pulmonary vascular disease.

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EFFECTS OF SURGERY ON PULMONARY FUNCTION

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Most of this paper consists of work done by Dr. L. A. G. Davidson in the immediately post-operative assessment of lung function following operations on the limbs, abdomen and thorax. The opening remarks (A. L. d'A.) will be of a cursory nature.

To predict what lung function will be after thoracic surgery is always in the nature of a gamble and may give rise to serious errors. It is surprising that we continue to take risks in thoracic surgery on patients whom we have not investigated pre-operatively to a sufficient degree from the point of view of respiratory physiology. It is indeed obvious that we often have far better physiological data available when we are about to open the chest for the correction of cardiac defects than when we are contemplating resection of considerable parts of the lung. Frequently, respiratory function studies may be of great help; if the whole of one lung is to be resected and that lung is functionless, as, for example, when it is totally airless as a result of carcinoma, one of the best tests may well be to assess the patient's degree of dyspnœa after climbing a flight of hospital stairs. Sometimes, however, the surgeon is not necessarily resecting the obviously functionless part of the lung and, if the contralateral lung is in a state of dubious health, then respiratory studies will be invaluable in telling us whether the patient will be unduly breathless subsequently or whether the surgeon should be prepared to do a tracheostomy, either before or at the end of the surgical intervention. These studies may be particularly valuable in (1) tuberculous patients, (2) cases of "air cysts" in patients who obviously have clinical emphysema, and (3) in patients with lung cancer. In the last group, as Professor Donald has said, a patient may prefer to be a respiratory cripple rather than lose his life and here considerable risks may be justifiable. If, however, the lung function tests show that such risks are really unjustifiable, such data will obviously be of great value.

It is not always possible to make assessments on a clinical basis. The surgery of pulmonary tuberculosis today may often involve resecting damaged tissue from both lungs. As Björk has shown, the patient subjected to resection may be carried through bilateral simultaneous surgery with a maximum breathing capacity of 30, provided he has a tracheostomy supplemented by aided respiration. Following the excision of damaged lung tissue, the maximum breathing capacity may show notable improvement and the patient may return to useful life.

When contemplating the removal of large air cysts, bronchospirometry or differential air sampling from each main bronchus may be of great value. If the lung function on the side containing the large air cyst is notably less than

that on the other side, removal of the cyst may allow the remaining lung tissue which is compressed by the cyst to regain a good deal of its lost function and such an operation may lead to a great improvement in respiratory function. In patients with carcinoma, where a lobe of the lung may be totally collapsed because of tumour at its bronchial orifice, the remaining lobe of the lung may be distended by entrapped air as a result of partial obstruction from the tumour. Such patients may be referred because of severe dyspnœa. Broncho-spirometry may indicate that removal of the affected lung, by getting rid of the area of air trapping, would lead to immediate relief of the dyspnœa. This relief is usually apparent on the first post-operative day.

Effects of Pneumonectomy on Lung Function

The removal of one lung by no means necessarily reduces lung function by 50 per cent. If the lung function is estimated six months after pneumonectomy for cancer or bronchiectasis the following findings are common:

1. The minute volume respiration is not significantly changed, as it is compensated for by a slight increase in the rate and depth of respiration.
2. The O_2 uptake remains approximately the same.
3. The maximum breathing capacity is reduced, but less than might be expected; it is often 80 per cent. of the pre-operative values, due perhaps to better co-ordination of the respiratory muscles and to the increase in the rate of respiration.
4. Respiratory reserve is decreased.
5. Gas mixing is improved because of the increase in ratio of effective tidal air to functional residual air.
6. In deep inspiration the total lung volume is greater than in a lung of comparable size because the mediastinum is more mobile.
7. Usually during strenuous exercise marked pulmonary hypertension develops.

In one of our patients, a professional sprinter who had had a pneumonectomy for bronchiectasis, his ability to run a hundred yards in just over eleven seconds was a remarkable achievement.

Lung Function after Collapse Operations or Lobectomy for Tuberculosis

The amazing results obtained by the modern treatment of pulmonary tuberculosis have greatly decreased the place of surgery. The discussion of what may happen to patients after thoracoplasty is not very relevant today. Gaensler's original work has now been confirmed many times. A further reference will be made to it in Dr. Davidson's section of this paper. Total ventilatory capacity estimated six months after an artificial pneumothorax is reduced by 30 per cent., whereas the loss after lobectomy may only be in the region of 15 per cent. Phrenic nerve paralysis leads to a loss of 10 to 15 per cent. The loss of total ventilatory capacity after thoracoplasty will naturally depend on the number of ribs removed. (See Fig. 2.)

Ankylosing Spondylitis

In this condition there are scarcely any chest wall movements at all. It is worth while remembering that thoracotomy on such a patient may interfere very little with the pre-existing lung physiology. Such patients may survive the removal of the whole or part of a lung for cancer with surprisingly little disturbance. On the other hand, an upper laparotomy, by greatly impairing the action of the abdominal muscles which play a large part in the respiratory function of these patients, may be a fatal procedure. Under these conditions, tracheostomy with aided respiration may be life-saving.

The ensuing part of this paper is the work of Dr. L. A. G. Davidson, who unfortunately was in the United States at the time of the Symposium.

The literature on this subject is so vast that we can no more than dip into it here and there, and I would like, therefore, to confine myself to three aspects of the subject, dealing first and very briefly with the effects of anæsthesia; secondly, with the mechanical effects of surgical interference; and thirdly, with the effects of operation on the efficiency of gas transfer across the lungs to the arterial blood.

Naturally central respiratory depressant drugs such as barbiturates and opiates (and indeed all the common anæsthetic agents except ether) depress respiration and result in hypoventilation. Peripherally acting muscle relaxants have a similar effect and occasionally the effects of these are unusually prolonged or the patient is more than usually sensitive to them, with the result that an acute state of hypoventilation with hypercarbia develops, as the patient recovers from the anæsthetic. These states respond to drug therapy or continued manual ventilation of the patient's lungs, with occasionally the necessity for mechanical ventilation for periods from a few hours up to a few days.

Much work has been done on the changes in acid base balance during and immediately after the operation, but there are so many variable factors, such as the actual drug used, position on the operating table and type of anæsthetic apparatus, that the results of such studies are difficult to interpret and often quite contradictory. In summary it may be said that respiratory acidosis follows the administration of all general anæsthetics except ether, unless ventilation is assisted, and, as you will see later, very often recurs after the patient has left the theatre even if acid base balance is normal at the end of the operation.

Ether may have a stimulant or depressant effect on respiration, depending on the combination of drugs in which it is used.

It is, however, generally agreed that the patient's normal acid base balance is restored within 24 hours no matter what type of anæsthesia is used.

The two main sections of this paper deal with some effects of surgery on, first, the mechanics of breathing and, secondly, on the pattern and physiological efficiency of respiration.

I would like to make it plain at this stage that surgical operations which do not enter a body cavity or interfere with the muscles used in respiration have no discernible effect on either the mechanics of the lungs or the efficiency of

gas transfer across them. In other words, modern anæsthesia has in itself virtually no after effects measurable after 24 hours (Table I).

However, as early as 1927 Churchill and McNeil showed that abdominal operations affected vital capacity and attempted to relate the degree of reduc-

TABLE I.—CONTROLS: NON-THORACIC NON-ABDOMINAL OPERATIONS
NINE PATIENTS

	pO_2 mm. Hg	pCO_2 mm. Hg	A-a gradient mm. Hg pO_2
Before operation ..	79·7	39·4	23·4
24 hours after operation	82·1	38·5	21·3
	V_A l/m.	RQ	F.E.V.* L./1 sec.
Before operation ..	4·65	0·848	2·08
24 hours after operation	5·08	0·839	2·09

* Five patients only.

tion in this parameter to the incidence of post-operative pulmonary complications. Many radiological and clinical surveys since have shown an incidence of such complications of 50 to 70 per cent. after abdominal surgery, and Bevan in a recent series from this hospital found, by daily serial X-rays, massive lobar or greater atelectasis in 35 per cent. of his 88 patients and recognisable segmental lesions in a further 20 per cent., a total of 55 per cent.

He attempted to relate the changes found to the degree of alteration of the

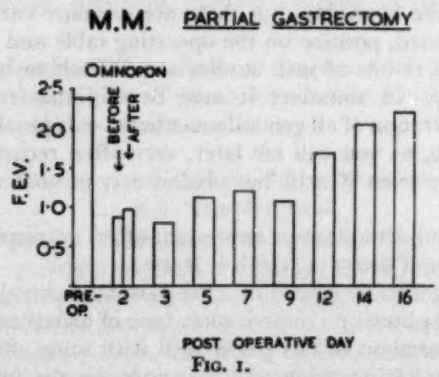

FIG. 1.

ventilatory capacity of the lungs as measured by the one-second Forced Expiratory Volume (F.E.V.) and found a good general correlation between the reduction in F.E.V. and both the incidence of pulmonary atelectasis and the presence and degree of pneumoperitoneum assessed radiologically.

The mean fall in F.E.V. in Bevan's series was to 40 per cent. of the pre-operative level; a figure almost identical with that found by Anscombe, whose monograph " The pulmonary complications of abdominal surgery " (1957) is well known.

Both these series relate to patients undergoing various operations requiring upper abdominal incisions. Lower abdominal incisions have less marked effects and, perhaps surprisingly, Bevan found that in a group of thoracic patients the reduction post-operatively of F.E.V. was only to 70 per cent. of the pre-operative value, *i.e.* only half as profound as in the abdominal operations.

The second figure shows a typical experiment of Bevan. Note the very slight improvement after an opiate (Fig. 1).

All authors agree that the alterations in pulmonary function post-operatively last 7 to 10 days.

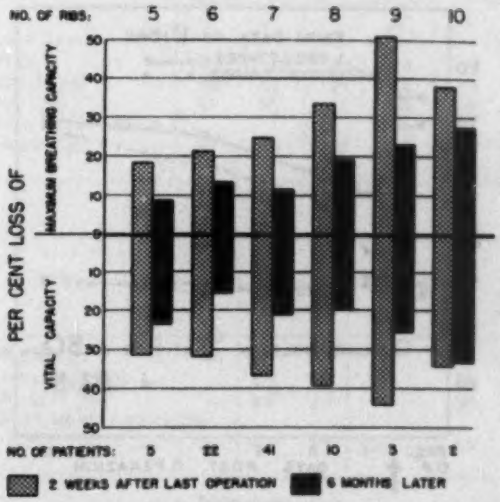

FIG. 2.

Anscombe further showed that surgical incisions in the abdomen produce a fall in all the measurable compartments of lung volume with a relative increase in the fraction, functional residual capacity/total volume.

Apart from the reduction in maximum expiratory *volume*, there is also a less marked reduction in maximum expiratory flow *rate*, and both factors are probably important in allowing or perpetuating atelectasis due to excessive bronchial secretions.

Whether abdominal operations have any permanent effect on the mechanics of breathing is not known, but unlikely. Many authors have shown that, in thoracic operations, reduction in the mechanical functional ability of the lungs is permanent and closely related to the amount of lung tissue removed or

rendered functionless. Fig. 2 is a typical diagram from a paper of Gaensler's showing how the reduction in vital capacity and M.B.C. is related to the extent of thoracoplasty and how improvement takes place in time. Finally, in this section a recent paper by Frank, Siebens and Newman has shown that pulmonary static compliance is reduced after removal of lung tissue and that this reduction also is directly related to the amount of lung tissue removed.

Tests of maximum attainable ventilation, while important in regard to the ability to cough and clear the bronchial tree of sputum, bear little relation to the ability to maintain normal resting levels of respiratory exchange and much less work has been devoted to this aspect of the problem.

Three groups of authors have reported a mean fall of 5 to 8 per cent. in arterial oxygen saturation post-operatively—Maier and Cournand (1943) in thoracic surgical patients, Carlsten, Norlander and Troell (1954) in abdominal surgical patients, and Mastio and Allbritten (1958) in a mixed group. Troell

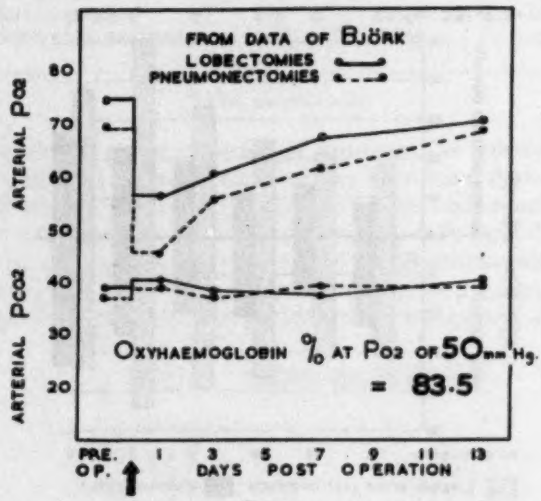

FIG. 3.

and his colleagues showed a 30 to 50 per cent. rise in cardiac output 24 hours post-operatively compared with the pre-operative values. The outputs were measured by the direct Fick method.

Five years ago Björk and Hilty (1954) published data from which the next figure is constructed, confirming the earlier results by blood gas tension estimates and suggesting that these effects, like the mechanical effects, lasted from 7 to 10 days. Note also here the confirmation of the restoration of acid base balance in 24 hours (Fig. 3).

One of the most sensitive indices of pulmonary function is the alveolo-arterial oxygen tension gradient (A-a gradient) calculated from the alveolar air equation and arterial blood gas tensions, and last year Ghord, Linderholm

and Norlander reported an increase in the A-a gradient 24 hours after abdominal operations both during air breathing and while breathing 100 per cent. oxygen. This increase was highly significant during one or other test, after anæsthesia by barbiturate-nitrous oxide relaxant; ether; or spinal methods. Acid base balance was unaffected at 24 hours compared with pre-operative values. The data from the 100 per cent. oxygen breathing suggested that the cause of the fall in arterial oxygen tensions (pO_2) was an increased venous admixture due to true shunts rather than an increase in areas of low ventilation-perfusion ratio.

Some of my own findings over the last two years are summarised in Table II. I have only given mean figures for simplicity. The first table shows that

TABLE II.—SUMMARY OF RESULTS

	pO_2 mm. Hg		pCO_2 mm. Hg		f 3 min.	
	B	*A*	*B*	*A*	*B*	*A*
Control (9)	80	82	39	39	50	57
Abdominal (20) ..	83	67	40	41	54	61
Thoracic (20)	80	67	41	44	60	77
Morphine after operation (9) ..	67	64	45	46	67	68

	V_A l/m.		*A-a gradient* mm. Hg pO_2	
	B	*A*	*B*	*A*
Control (9)	4·7	5·1	23	21
Abdominal (20)	4·3	3·5	22	29
Thoracic (20)	4·8	4·6	26	30
Morphine after operation (9)	4·2*	3·0	39*	35

B = Before operation.
A = After operation.
* = 4 patients only.

considerable alveolar underventilation developed in the first hour after the operation even though the " end operation " figure for pCO_2 was the same as before operation. Alveolar ventilation had returned to normal by six hours. This hypoventilation is very common and is reported in 25 per cent. of consecutive routine general surgical patients by Hamilton and Devine in 1957.

The second table summarises my results by type of operation. This table compares the findings on the day before with those 24 hours after the operation.

I believe the type of operation performed is much more important than the type of anæsthesia, and the most profound changes are found with upper

abdominal incisions, then with thoracic incisions, and then lower abdominal incisions, and then note that extra cœlomic operations are without effect except on the pattern of breathing.

These changes occurred in almost every case, including a patient who had an extra-pleural intra-thoracic lipoma removed through a fifth intercostal space incision without opening the pleura, and a young man who had an upper laparotomy without any intra-abdominal operation. The only exceptions not showing a fall in PO_2 were in the thoracic group, where in 2 patients the post-operative changes were more than compensated by the removal of perfused but non-ventilated lung tissue at the operation. It is interesting to note also that in a group of 9 patients the effect of 15 mg. of morphine sulphate over one hour was negligible. (The fall in alveolar ventilation is almost solely due to Cheyne-Stokes respiration in one patient with a very low recorded ventilation.)

Treating the group as a whole including the control series, there was a significant change in the pattern of breathing as compared to before operation.

The tidal volume was decreased by 13 per cent. with more than complete compensation in the shape of an increase in respiratory rate of 20 per cent. resulting in the maintenance of alveolar ventilation and therefore of CO_2 homeostasis.

This pattern fits in with Anscombe's and with Brättstrom's finding of a reduced nitrogen wash-out time in 200 post-operative patients, *i.e.* a smaller alveolar volume is flushed more frequently to maintain CO_2 homeostasis.

In the controls, surgery did not alter arterial blood oxygen tension (PO_2), but a significant fall in PO_2 was found in the thoracic and upper abdominal incision groups and also in the patients with lower abdominal incisions, although here the fall, like the fall in F.E.V., was not quite so marked.

These falls in PO_2 were not in the group-means sufficient to reduce arterial saturation below 90 per cent., but in individual cases falls of saturation of up to 15 per cent. were recorded.

There was a significant increase in A-a gradient in both thoracic and abdominal patients indicating an increased venous admixture effect. Venous admixture was double the pre-operative value and was probably in the region of 25 per cent. of the cardiac output.

The high pre-operative values for A-a gradients are due partly to the patients being tested sitting propped up in bed and partly to the high incidence of bronchitis in the general population in Birmingham.

My data cannot by their nature confirm Linderholm's (1958) finding of true shunts on high oxygen breathing, but give no support to the suggestion that hypoventilation is the main cause of the fall in PO_2 and saturation after operation.

This fall appears to be due either to regional changes in distribution of inspired gas with the development of areas of low ventilation-perfusion ratios or more likely to a true shunt effect, *i.e.* areas of atelectasis not detectable clinically or radiologically. The latter concept fits in with Linderholm's findings on high oxygen breathing, and with the low functional residual volume, reduced nitrogen wash-out time and lack of change in physiological dead space.

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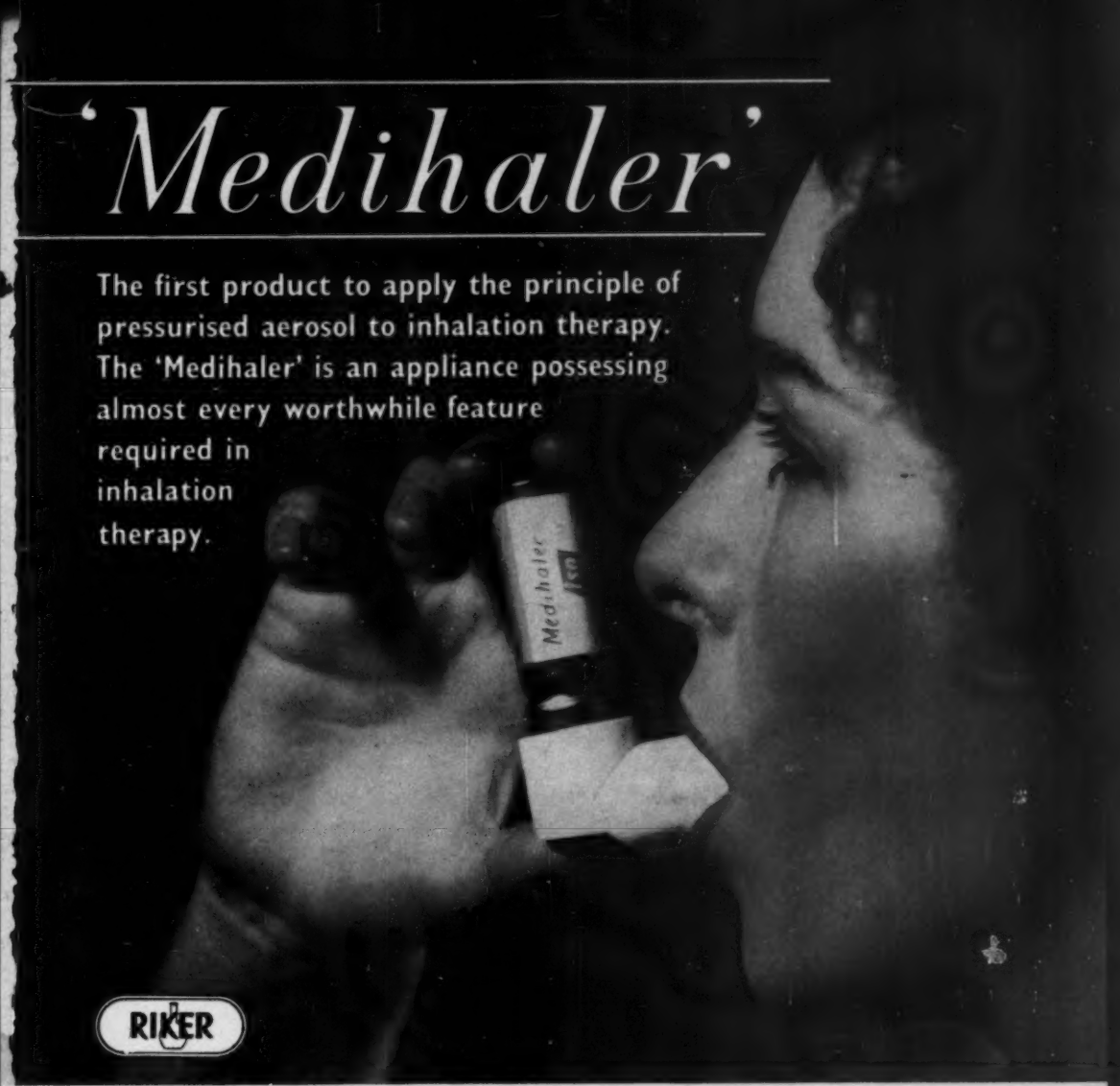

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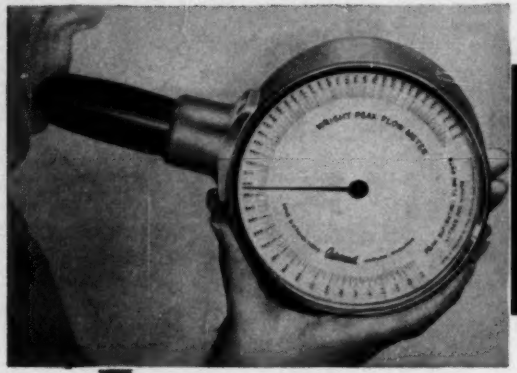

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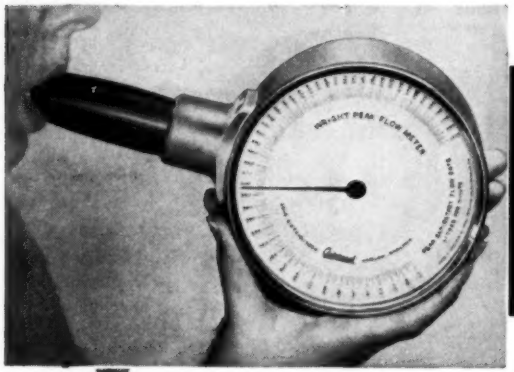

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